# SEARCH REQUEST FORM

**Scientific and Technical Information Center**

Requester's Full Name: Lakshmi Channavajjala Examiner #: 74459 Date: 4-7-02

Art Unit: 1615 Phone Number 308-2438 Serial Number: 09/917,858

Mail Box and Bldg/Room Location: 2B01, CM1 Results Format Preferred (circle): PAPER DISK E-MAIL

07 : CM1 - 2B05

**If more than one search is submitted, please prioritize searches in order needed.**

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Use of moxonidine for Postmyocardial infarction treatment

Inventors (please provide full names): Regina Schoemaker

Earliest Priority Filing Date: 2/1/1999

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

1) Please search for the compound of claim 1, which is also called moxonidine. 75438-57-2 norcynt nucynt moxon

2) Please search (1) and (myocardial infarction or myocardial cynt damage or Post myocardial or ischemic myocardium or heart muscle necrosis or thrombolytic or fibrinolytic therapy or reperfusion or reperfusing ~~therapy~~ or myocardial heart failure Or myocardial hypertrophy or Sympathetic nervous System or heart failure or Cardiac hypertrophy).

Please display results chanks

Rsh Search Approved TK Page, SPE, AU 1615 Lakshmi

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**STAFF USE ONLY**

Searcher: Mary

Searcher Phone #: X4258

Searcher Location:

Date Searcher Picked Up:

Date Completed: 4/2

Searcher Prep & Review Time:

Clerical Prep Time:

Online Time: 4/3

**Type of Search**

NA Sequence (#)

AA Sequence (#)

Structure (#) 1

Bibliographic

Litigation

Fulltext

Patent Family

Other

**Vendors and cost where applicable**

STN 687.69

Dialog

Questel/Orbit

Dr.Link

Lexis/Nexis

Sequence Systems

WWW/Internet

Other (specify)

PTO-1590 (8-01)

Channavajjala
917858

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=> d l3 que stat;d 1-27 ide cbib abs
L1                  STR
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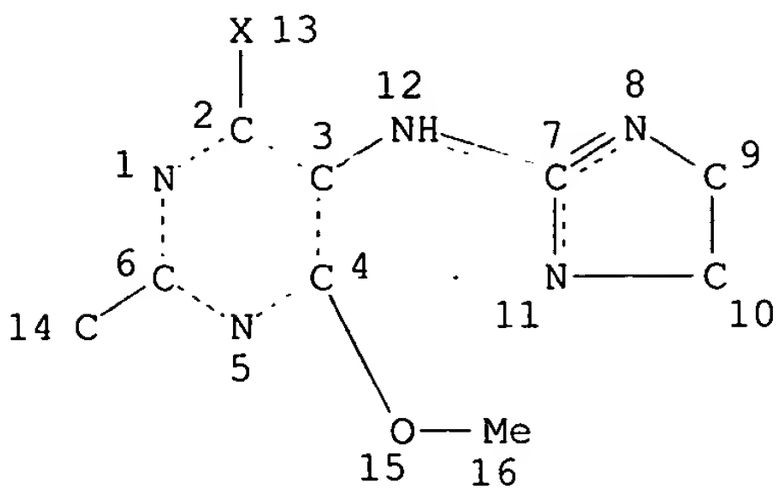


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE
L3            27 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED     34 ITERATIONS                          27 ANSWERS
SEARCH TIME: 00.00.01



L3   ANSWER 1 OF 27  REGISTRY  COPYRIGHT 2002 ACS
RN   357927-61-8  REGISTRY
CN   5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-
     methyl-, conjugate monoacid (9CI)  (CA INDEX NAME)
MF   C9 H12 Cl N5 O . H
SR   CA
LC   STN Files:   CA, CAPLUS
CRN  (75438-57-2)
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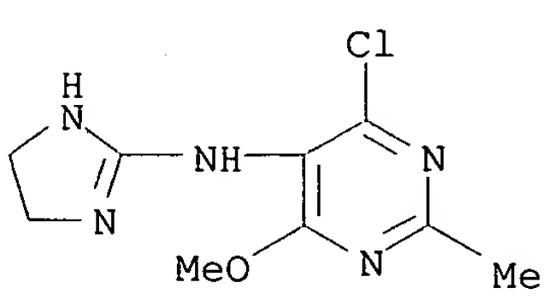


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                1 REFERENCES IN FILE CA (1967 TO DATE)
                1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE  1:  135:210719  Theoretical Study of Molecular Structure,
     Tautomerism, and Geometrical Isomerism of Moxonidine: Two-Layered ONIOM
     Calculations.  Remko, Milan; Walsh, Owen A.; Richards, W. Graham

Searched by: Mary Hale 308-4258 CM-1 12D16
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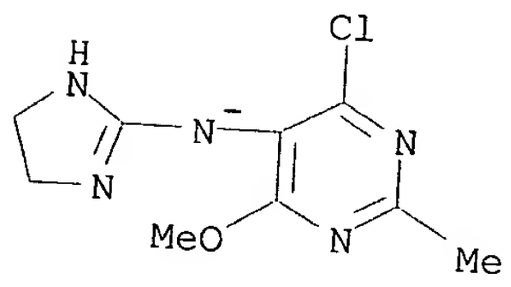
(Department of Pharmaceutical Chemistry, Comenius University, Bratislava, SK-832 32, Slovakia). Journal of Physical Chemistry A, 105(28), 6926-6931 (English) 2001. CODEN: JPCAFH. ISSN: 1089-5639. Publisher: American Chemical Society.

AB The geometries of various tautomers and rotamers of moxonidine (I) in both anionic and protonated forms were optimized using the two-layered ONIOM(B3LYP 6-311+G(d,p): AM1) method. The calcns. showed that, in agreement with expts., I exists in a more stable imino tautomer. The tautomer contg. the amino group is less stable by about 19 kJ/mol. The computed stable conformation for the I species is characterized by the pyrimidine and imidazolidine rings being in the mutual gauche conformation to one another. In contrast to the parent neutral mol. of I, ionization caused considerable geometric changes in the anions compared to the neutral species. In the neutral form and anion of the parent drug, an intramol. hydrogen bond stabilizes the structure and makes the most stable conformations more planar. The primary protonation site is the imidazolidine part of drug. The proton affinity of I was computed to be -1004 kJ/mol. I was found to be less lipophilic than the base of parent clonidine.

L3 ANSWER 2 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 357927-60-7 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, ion(1-) (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H11 Cl N5 O
SR CA
LC STN Files: CA, CAPLUS




1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:210719 Theoretical Study of Molecular Structure, Tautomerism, and Geometrical Isomerism of Moxonidine: Two-Layered ONIOM Calculations. Remko, Milan; Walsh, Owen A.; Richards, W. Graham (Department of Pharmaceutical Chemistry, Comenius University, Bratislava, SK-832 32, Slovakia). Journal of Physical Chemistry A, 105(28), 6926-6931 (English) 2001. CODEN: JPCAFH. ISSN: 1089-5639. Publisher: American Chemical Society.

AB The geometries of various tautomers and rotamers of moxonidine (I) in both anionic and protonated forms were optimized using the two-layered ONIOM(B3LYP 6-311+G(d,p): AM1) method. The calcns. showed that, in agreement with expts., I exists in a more stable imino tautomer. The tautomer contg. the amino group is less stable by about 19 kJ/mol. The computed stable conformation for the I species is characterized by the pyrimidine and imidazolidine rings being in the mutual gauche conformation to one another. In contrast to the parent neutral mol. of I, ionization caused considerable geometric changes in the anions compared to the neutral species. In the neutral form and anion of the parent drug, an intramol. hydrogen bond stabilizes the structure and makes the most stable conformations more planar. The primary protonation site is the imidazolidine part of drug. The proton affinity of I was computed to be -1004 kJ/mol. I was found to be less lipophilic than the base of parent

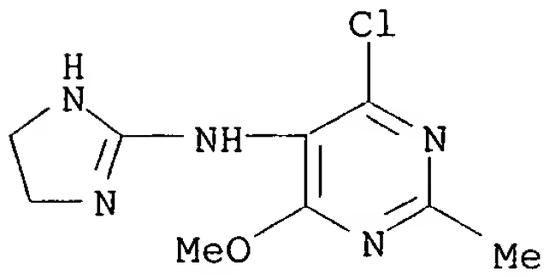
Searched by: Mary Hale 308-4258 CM-1 12D16

clonidine.

L3 ANSWER 3 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-46-1 REGISTRY
CN Octadecanoic acid, compd. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, monooctadecanoate (9CI)
MF C18 H36 O2 . C9 H12 Cl N5 O
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

CRN 57-11-4
CMF C18 H36 O2

$HO_2C-(CH_2)_{16}-Me$

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.
AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 4 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-45-0 REGISTRY

Searched by: Mary Hale 308-4258 CM-1 12D16

CN 2-Naphthalenecarboxylic acid, 4,4'-methylenebis[3-hydroxy-, compd. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (1:2) (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylate] (2:1) (9CI)

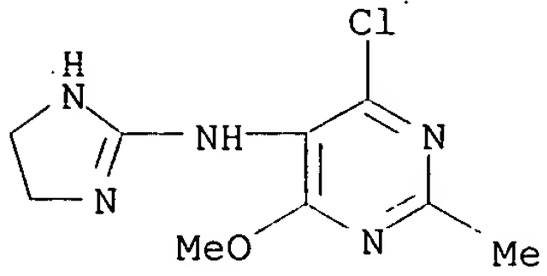
MF C23 H16 O6 . 2 C9 H12 Cl N5 O

SR CA

LC STN Files: CA, CAPLUS

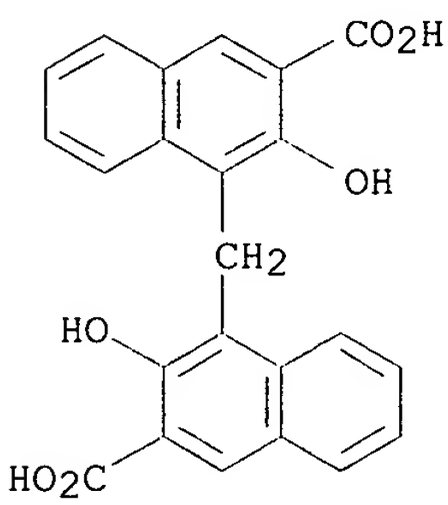
CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

CRN 130-85-8
CMF C23 H16 O6




1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left

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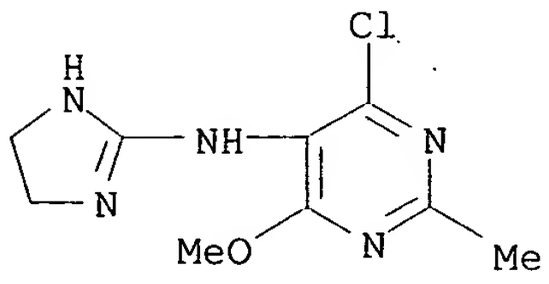
ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 5 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-44-9 REGISTRY
CN 2-Naphthalenecarboxylic acid, 4,4'-methylenebis[3-hydroxy-, compd. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylate] (1:1) (9CI)
MF C23 H16 O6 . C9 H12 Cl N5 O
SR CA
LC STN Files: CA, CAPLUS

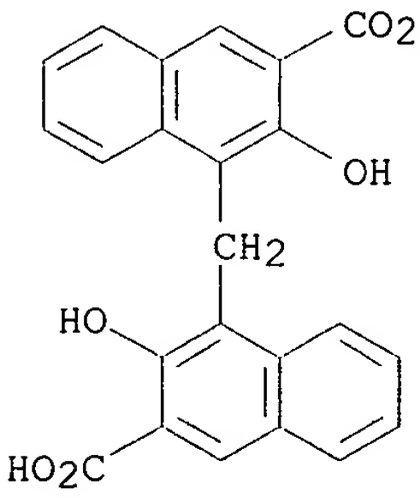
CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

CRN 130-85-8
CMF C23 H16 O6




1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF,

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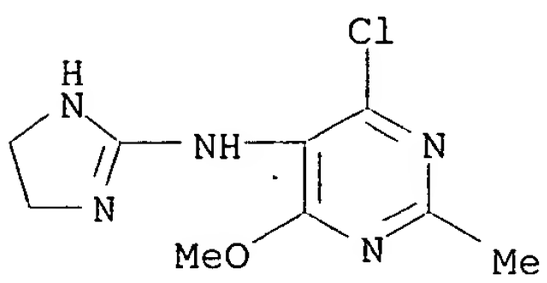
BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 6 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-43-8 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, monobenzoate (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . C7 H6 O2
SR CA
LC STN Files: CA, CAPLUS

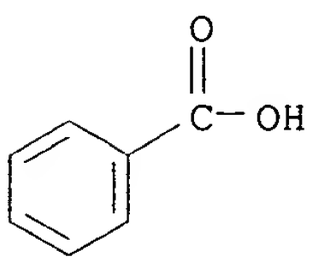
CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

CRN 65-85-0
CMF C7 H6 O2




1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.

Searched by: Mary Hale 308-4258 CM-1 12D16

APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 7 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-41-6 REGISTRY
CN Hexanedioic acid, compd. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (1:2) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, hexanedioate (2:1) (9CI)
MF C9 H12 Cl N5 O . 1/2 C6 H10 O4
SR CA
LC STN Files: CA, CAPLUS

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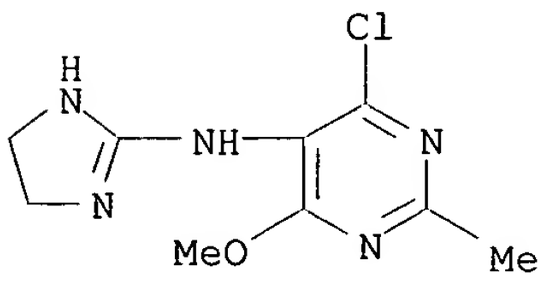
CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

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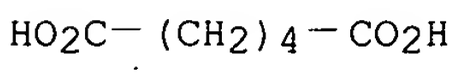


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

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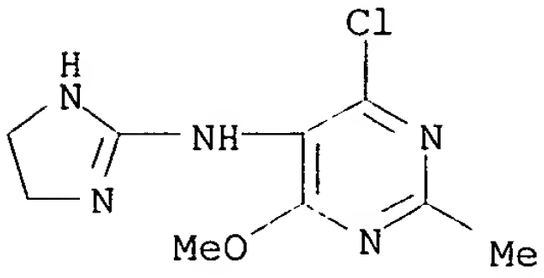
Searched by: Mary Hale 308-4258 CM-1 12D16

prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 8 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-40-5 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, ethanedioate (1:1) (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . C2 H2 O4
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O



CM 2

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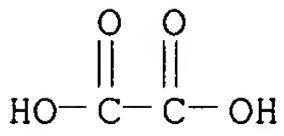


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

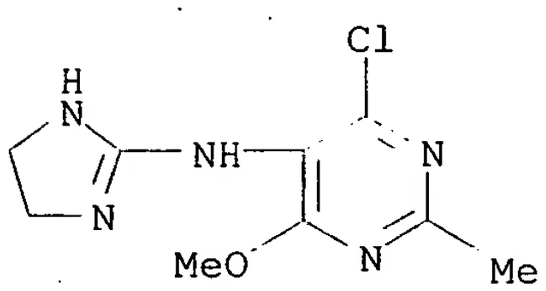
AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

Searched by: Mary Hale 308-4258 CM-1 12D16

L3 ANSWER 9 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-39-2 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, ethanedioate (2:1) (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . 1/2 C2 H2 O4
SR CA
LC STN Files: CA, CAPLUS

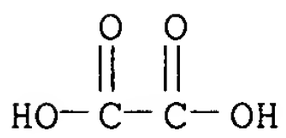
CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O



CM 2

CRN 144-62-7
CMF C2 H2 O4



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

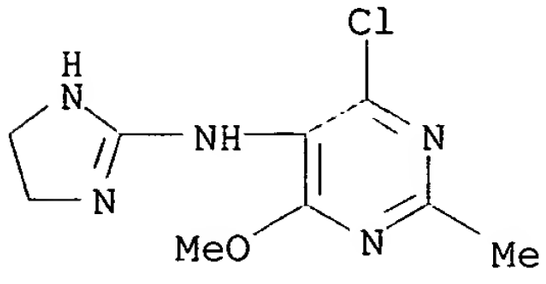
L3 ANSWER 10 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-38-1 REGISTRY
CN Butanedioic acid, compd. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (1:2) (9CI) (CA INDEX NAME)

Searched by: Mary Hale 308-4258 CM-1 12D16

OTHER CA INDEX NAMES:
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, butanedioate (2:1) (9CI)
MF C9 H12 Cl N5 O . 1/2 C4 H6 O4
SR CA
LC STN Files: CA, CAPLUS

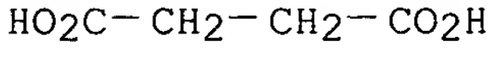
CM 1

CRN 75438-57-2
CMF C9 H12 Cl N5 O




CM 2

CRN 110-15-6
CMF C4 H6 O4



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

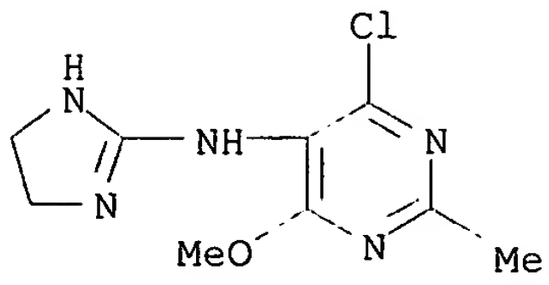
AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 11 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-37-0 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, (2E)-2-butenedioate (2:1) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C9 H12 Cl N5 O . 1/2 C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS

Searched by: Mary Hale 308-4258 CM-1 12D16

CM 1

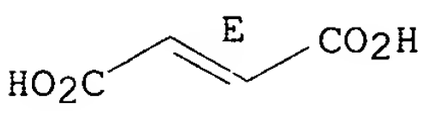
CRN 75438-57-2
CMF C9 H12 Cl N5 O



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

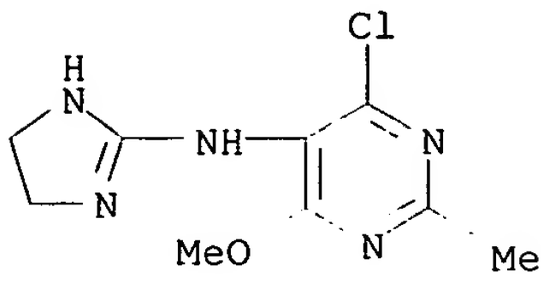
L3 ANSWER 12 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-36-9 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C9 H12 Cl N5 O . 1/2 C4 H6 O6
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 75438-57-2

Searched by: Mary Hale 308-4258 CM-1 12D16

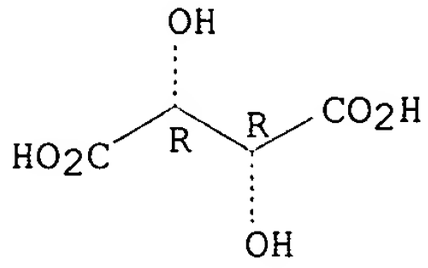
CMF C9 H12 Cl N5 O



CM 2

CRN 87-69-4
CMF C4 H6 O6

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

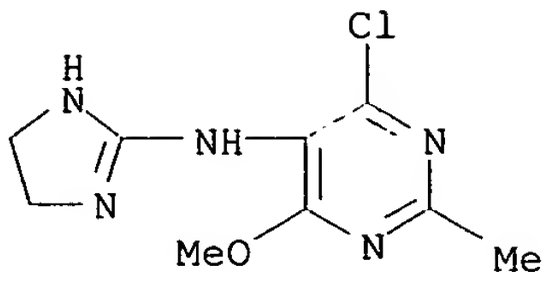
AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 13 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-35-8 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, sulfate (2:1) (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . 1/2 H2 O4 S
SR CA
LC STN Files: CA, CAPLUS

CM 1

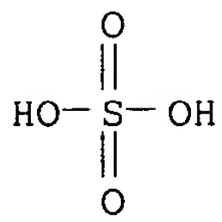
CRN 75438-57-2
CMF C9 H12 Cl N5 O

Searched by: Mary Hale 308-4258 CM-1 12D16



CM 2

CRN 7664-93-9
CMF H2 O4 S



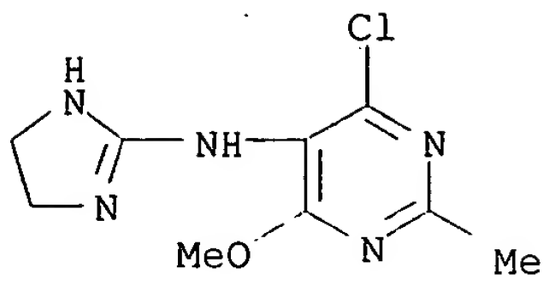
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 14 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 287099-34-7 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, hydrochloride, monohydrate (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . x Cl H . H2 O
SR CA
LC STN Files: CA, CAPLUS
CRN (75438-57-2)

Searched by: Mary Hale 308-4258 CM-1 12D16



● x HCl

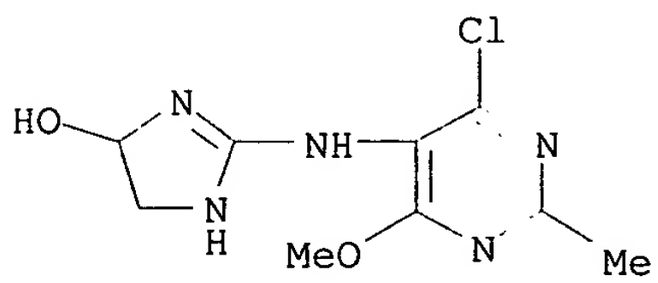
● $H_2O$

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:155425 Moxonidine salts for sustained release. Anderson, Neil Robert; Wirth, David Dale (Eli Lilly and Company, USA). PCT Int. Appl. WO 2000044355 A1 20000803, 39 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US968 20000114. PRIORITY: US 1999-PV117981 19990129.

AB This invention comprises a low soly. salt of moxonidine and pharmaceutical formulations, contg. a low soly. moxonidine salt, for the sustained release of moxonidine. The invention further discloses methods for prophylactically or therapeutically treating hypertension or left ventricular hypertrophy comprising with the sustained release, low soly. moxonidine pharmaceutical formulation. Salts such as L-tartrate, fumarate, pamoate, succinate, oxalate and benzoate were prepd. and their solubilities were less than moxonidine itself.

L3 ANSWER 15 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-34-8 REGISTRY
CN 1H-Imidazol-4-ol, 2-[(4-chloro-6-methoxy-2-methyl-5-pyrimidinyl)amino]-4,5-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H12 Cl N5 O2
SR CA
LC STN Files: CA, CAPLUS



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

Searched by: Mary Hale 308-4258 CM-1 12D16

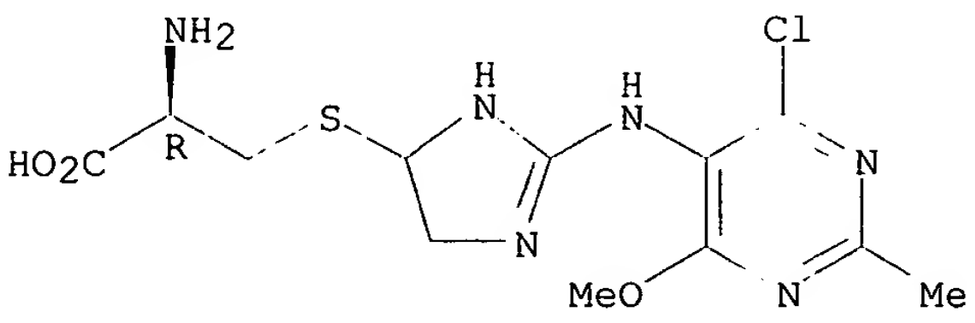
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 16 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-31-5 REGISTRY
CN L-Cysteine, S-[2-[(4-chloro-6-methoxy-2-methyl-5-pyrimidinyl)amino]-4,5-dihydro-1H-imidazol-4-yl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C12 H17 Cl N6 O3 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

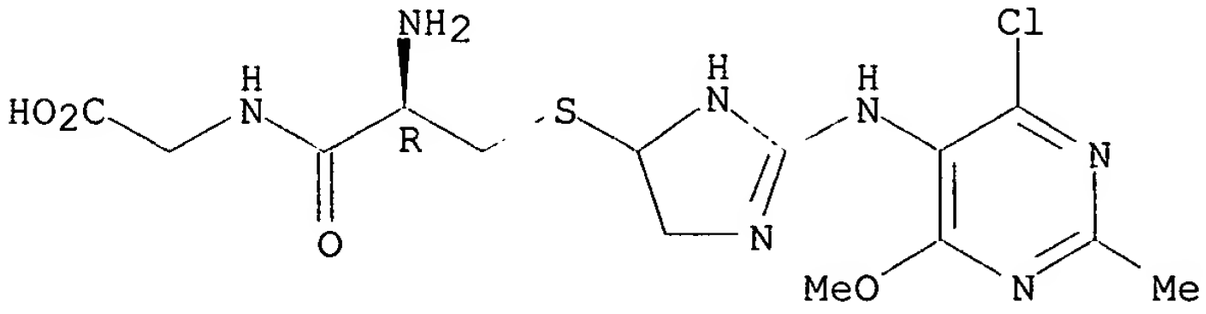
Searched by: Mary Hale 308-4258 CM-1 12D16

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 17 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-28-0 REGISTRY
CN Glycine, S-[2-[(4-chloro-6-methoxy-2-methyl-5-pyrimidinyl)amino]-4,5-dihydro-1H-imidazol-4-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C14 H20 Cl N7 O4 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer

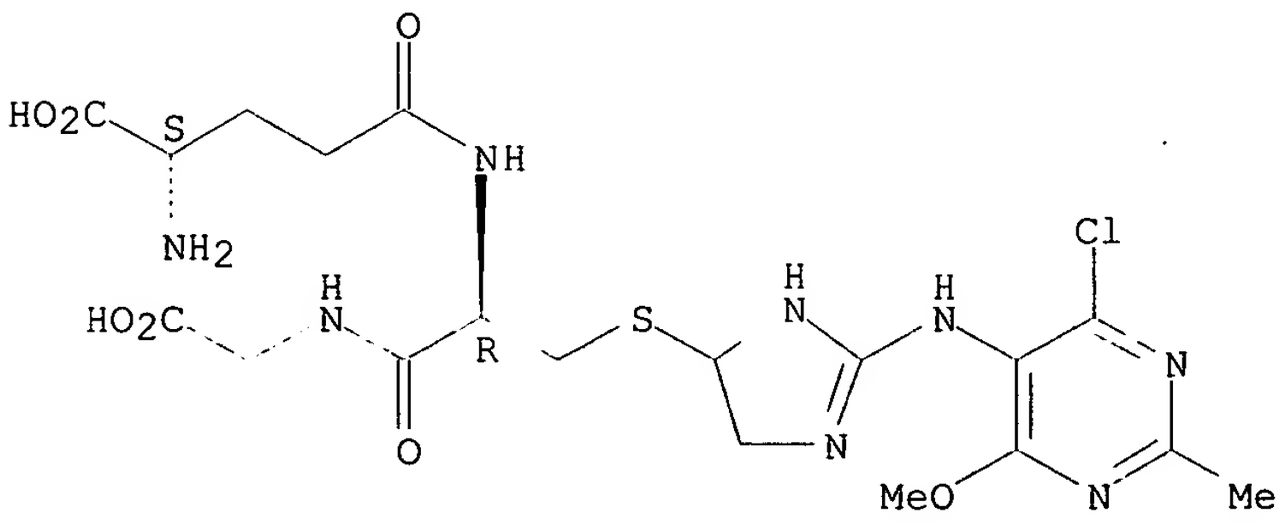
Searched by: Mary Hale 308-4258 CM-1 12D16

344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 18 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-25-7 REGISTRY
CN Glycine, L-.gamma.-glutamyl-S-[2-[(4-chloro-6-methoxy-2-methyl-5-pyrimidinyl)amino]-4,5-dihydro-1H-imidazol-4-yl]-L-cysteinyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C19 H27 Cl N8 O7 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

Searched by: Mary Hale 308-4258 CM-1 12D16

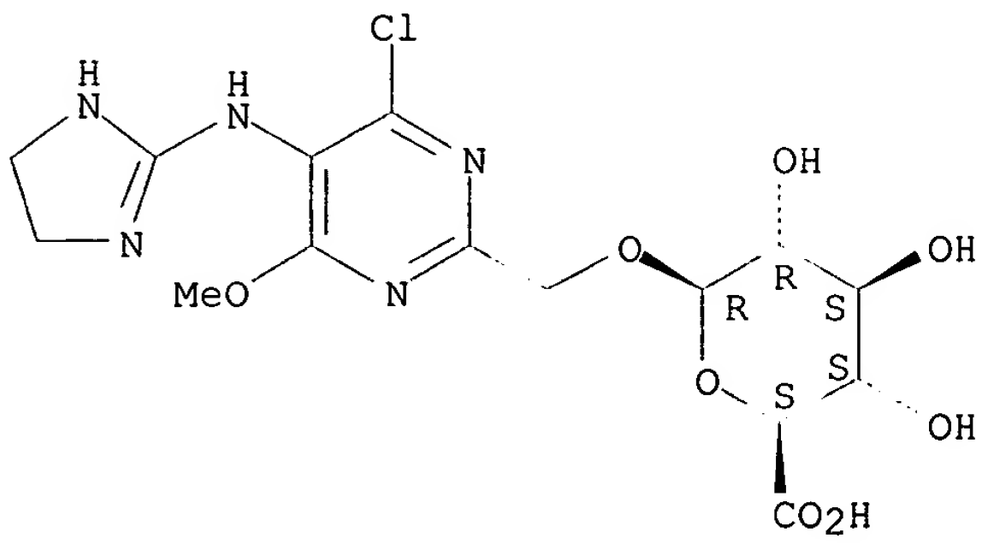
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 19 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-23-5 REGISTRY
CN .beta.-D-Glucopyranosiduronic acid, [4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)amino]-6-methoxy-2-pyrimidinyl]methyl (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H20 Cl N5 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.




Searched by: Mary Hale 308-4258 CM-1 12D16

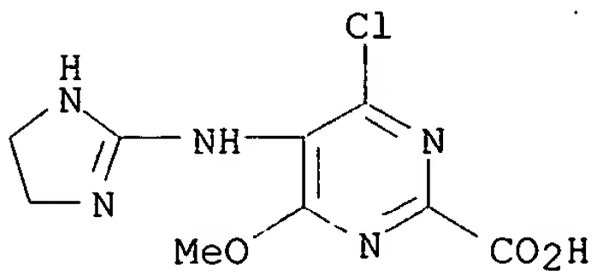
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 20 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 272114-22-4 REGISTRY
CN 2-Pyrimidinecarboxylic acid, 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)amino]-6-methoxy- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H10 Cl N5 O3
SR CA
LC STN Files: CA, CAPLUS




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

1 REFERENCES IN FILE CA (1967 TO DATE)

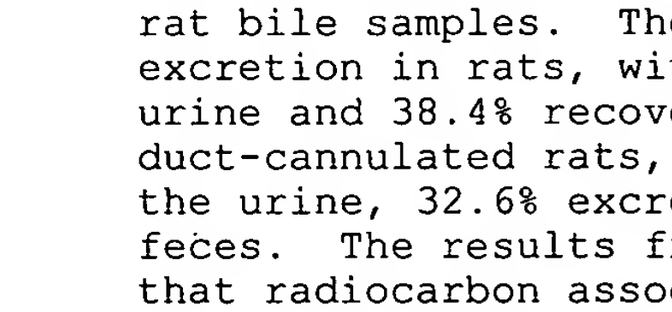
Searched by: Mary Hale 308-4258 CM-1 12D16

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

L3 ANSWER 21 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 220951-60-0 REGISTRY
CN 2-Pyrimidinemethanol, 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)amino]-6-methoxy- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-Hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxypyrimidine
FS 3D CONCORD
MF C9 H12 Cl N5 O2
SR CA
LC STN Files: CA, CAPLUS




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

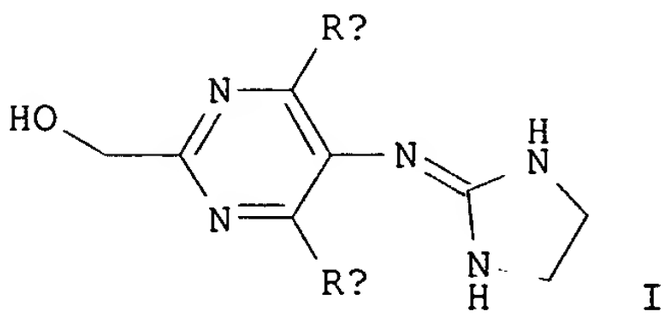
Searched by: Mary Hale 308-4258 CM-1 12D16

REFERENCE 1: 133:12324 Metabolism and disposition of moxonidine in fischer 344 rats. He, Minxia M.; Abraham, Trent L.; Lindsay, Thomas J.; Chay, Sylvia H.; Czeskis, Boris A.; Shipley, Lisa A. (Department of Drug Metabolism and Disposition, Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA). Drug Metabolism and Disposition, 28(4), 446-459 (English) 2000. CODEN: DMDSAI. ISSN: 0090-9556. Publisher: American Society for Pharmacology and Experimental Therapeutics.

AB The metab. and disposition of moxonidine (4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxy-2-methylpyrimidine), a potent central-acting antihypertensive agent, were investigated in F344 rats. After an i.v. or oral administration of 0.3 mg/kg of [14C]moxonidine, the max. plasma concns. of moxonidine were detd. to be 146.0 and 4.0 ng/mL, resp., and the elimination half-lives were 0.9 and 1.1 h, resp. The oral bioavailability of moxonidine was detd. to be 5.1%. The metabolic and elimination profiles of moxonidine were detd. after an oral administration of 5 mg/kg of [14C]moxonidine. More than fifteen phase I and phase II metabolites of moxonidine were identified in the different biol. matrixes (urine, plasma, and bile). Oxidative metab. of moxonidine leads to the formation of hydroxymethyl moxonidine and a carboxylic acid metabolite as the major metabolites. Several GSH conjugates, cysteinylglycine conjugates, cysteine conjugates, and a glucuronide conjugate were also identified in rat bile samples. The radiocarbon was eliminated primarily by urinary excretion in rats, with 59.5% of total radioactivity recovered in the urine and 38.4% recovered in the feces within 120 h. In bile duct-cannulated rats, about 39.7% of the radiolabeled dose was excreted in the urine, 32.6% excreted in the bile, and approx. 2% remained in the feces. The results from a quant. whole body autoradiog. study indicate that radiocarbon assocd. with [14C]moxonidine and/or its metabolites was widely distributed to tissues, with the highest levels of radioactivity obsd. in the kidney and liver. In summary, moxonidine is well absorbed, extensively metabolized, widely distributed into tissues, and rapidly eliminated in rats after oral administration.

REFERENCE 2: 130:209719 Preparation of imidazolidinylideneaminopyrimidines for treatment of hypertension, congestive heart failure, atherosclerosis, drug withdrawal, and non-insulin dependent diabetes.. Abraham, Trent Lee; Czeskis, Boris Arnoldovich; He, Minxia; Shipley, Lisa Ann (Eli Lilly and Company, USA). PCT Int. Appl. WO 9911269 A1 19990311, 29 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18381 19980903. PRIORITY: US 1997-57472 19970903.

GI




I

AB Title compds. (I; Ra, Rb = halo, alkoxy), and esters or amides thereof,

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were prepd. Thus, hydroxyacetamidine hydrochloride was stirred 5 min. in EtOH contg. NaOEt; Et malonate was added and the mixt. was refluxed 3 h to give 79% 4,6-dihydroxy-2-hydroxymethylpyrimidine. This was stirred with fuming HNO3/AcOH to give 80.5% 4,6-dihydroxy-2-hydroxymethyl-5-nitropyrimidine, which was heated with AcOH/Ac2O at 105.degree. for 2 h to give 99% 2-acetoxymethyl-4,6-dihydroxy-5-nitropyrimidine. The latter was refluxed 2 h with POCl3 and PhNEt2 to give 77% 2-acetoxymethyl-4,6-dichloro-5-nitropyrimidine, which was hydrogenated in EtOH over Raney Ni to give 89% 2-acetoxymethyl-4,6-dichloro-5-aminopyrimidine. Treatment of the amine with N-acetyl-2-imidazolidone and POCl3 at 105-110.degree. for 3 h gave 59% 2-acetoxymethyl-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)pyrimidine. The latter was refluxed with NaOMe in MeOH to give 50% 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxypyrimidine. The latter reduced blood pressure and heart rate in rats.

L3 ANSWER 22 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 125727-52-8 REGISTRY
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide, mixt. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine and 6-phenyl-2,4,7-pteridinetriamine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,4,7-Pteridinetriamine, 6-phenyl-, mixt. contg. (9CI)
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, mixt. contg. (9CI)
MF C12 H11 N7 . C9 H12 Cl N5 O . C7 H8 Cl N3 O4 S2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL

CM 1

CRN 75438-57-2
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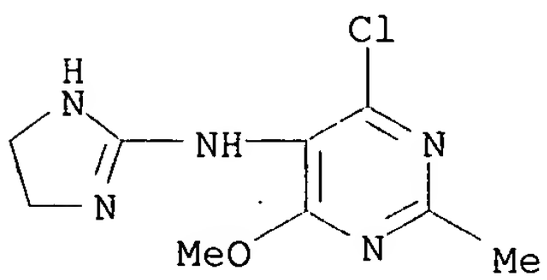
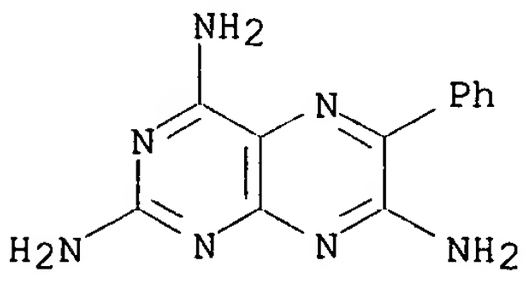



CM 2

CRN 396-01-0
CMF C12 H11 N7




CM 3

Searched by: Mary Hale 308-4258 CM-1 12D16

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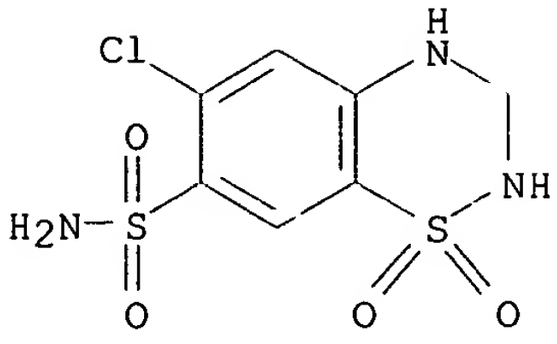

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 112:125204 Moxonidine- and hydrochlorothiazide-containing synergistic diuretics and antihypertensives. Armah, Ben; Stenzel, Wolfgang; Plaenitz, Vera (Beiersdorf A.-G., Fed. Rep. Ger.). Eur. Pat. Appl. EP 317855 A2 19890531, 8 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE. (German). CODEN: EPXXDW. APPLICATION: EP 1988-118906 19881112. PRIORITY: DE 1987-3739779 19871124.

AB Compns. comprising moxonidine, or its salt, hydrochlorothiazide, and, optionally, triamterene, are synergistic diuretic and antihypertesive drugs, esp. suitable for long-term treatment. The drugs are usable for the treatment of edema, cardiac insufficiency, arterial hypertonia, etc. Combined oral administration of 3 mg moxonidine and 30 mg hydrochlorothiazide/kg, synergistically decreased the systolic blood pressure of genetically hypertensive rats. Tablets comprised moxonidine 0.1, hydrochlorothiazide 6.25, lactose 87.25, PVP 1, starch 5 and FST-complex 0.4 mg.

L3 ANSWER 23 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 125727-51-7 REGISTRY
CN 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide, mixt. with 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidinamine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, mixt. contg. (9CI)
MF C9 H12 Cl N5 O . C7 H8 Cl N3 O4 S2
CI MXS
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL

CM 1

CRN 75438-57-2
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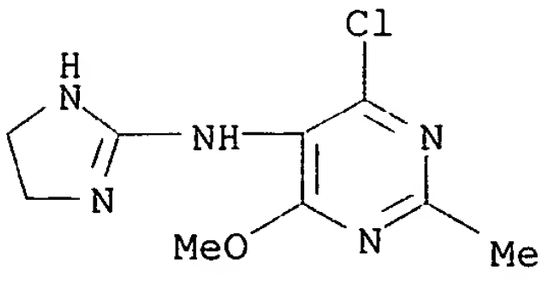

Searched by: Mary Hale 308-4258 CM-1 12D16

CM 2

CRN 58-93-5
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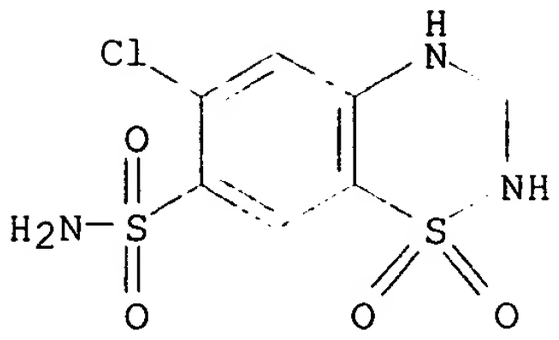
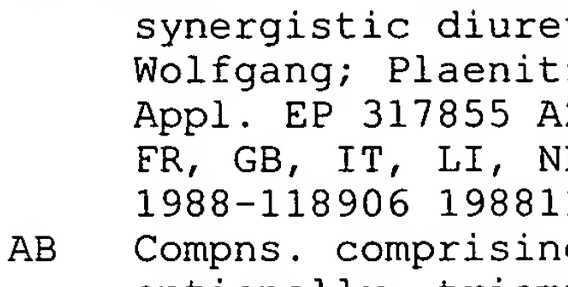


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 112:125204 Moxonidine- and hydrochlorothiazide-containing synergistic diuretics and antihypertensives. Armah, Ben; Stenzel, Wolfgang; Plaenitz, Vera (Beiersdorf A.-G., Fed. Rep. Ger.). Eur. Pat. Appl. EP 317855 A2 19890531, 8 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE. (German). CODEN: EPXXDW. APPLICATION: EP 1988-118906 19881112. PRIORITY: DE 1987-3739779 19871124.

AB Compns. comprising moxonidine, or its salt, hydrochlorothiazide, and, optionally, triamterene, are synergistic diuretic and antihypertesive drugs, esp. suitable for long-term treatment. The drugs are usable for the treatment of edema, cardiac insufficiency, arterial hypertonia, etc. Combined oral administration of 3 mg moxonidine and 30 mg hydrochlorothiazide/kg, synergistically decreased the systolic blood pressure of genetically hypertensive rats. Tablets comprised moxonidine 0.1, hydrochlorothiazide 6.25, lactose 87.25, PVP 1, starch 5 and FST-complex 0.4 mg.

L3 ANSWER 24 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 75536-04-8 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, monohydrochloride (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . Cl H
LC STN Files: CA, CAPLUS, CASREACT, DRUGPAT, DRUGUPDATES, USPATFULL
CRN (75438-57-2)



● HCl

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:107295 Synthesis of antihypertensive moxonidine. Wu, Yiwen; Mei, Heshan; Zhang, Zhongmin; Lu, Xinying; Yan, Tingren (Pharmaceutical College, Hebei Medical University, Shijiazhuang, 050017,

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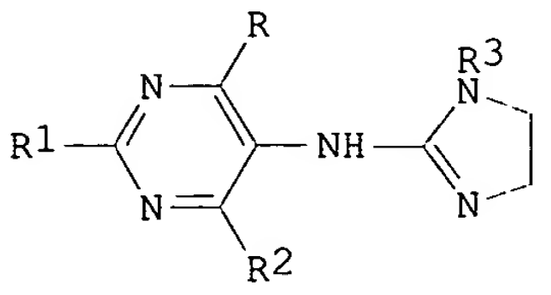
Peop. Rep. China). Zhongguo Yaowu Huaxue Zazhi, 11(1), 45-46 (Chinese) 2001. CODEN: ZYHZEF. ISSN: 1005-0108. Publisher: Zhongguo Yaowu Huaxue Zazhi Bianjibu.

AB Moxonidine was synthesized from acetamidine hydrochloride by cyclizing with di-Et malonate in the presence of Na ethoxide under refluxing for 3 h, nitrifying, chlorinating with POCl3, reducing with Fe/HCl, adding and hydrogenating with 1-acetyl-2-imidazolidone, and methanolysis. The overall yield was 24.8%. The yield of chlorination was 92.8% by using phosphorus oxychloride as the chlorinating agent. The yield of redn. was 87.7% by using iron powder as the reductant and steam distn. as sepn. method.

REFERENCE 2: 93:220769 Substituted 5-(2-imidazolin-2-yl)aminopyrimidines. Stenzel, Wolfgang; Fleck, Wolfgang; Cohnen, Erich; Armah, Ben (Beiersdorf A.-G., Fed. Rep. Ger.). Ger. Offen. DE 2849537 19800522, 16 pp. (German). CODEN: GWXXBX. APPLICATION: DE 1978-2849537 19781115.

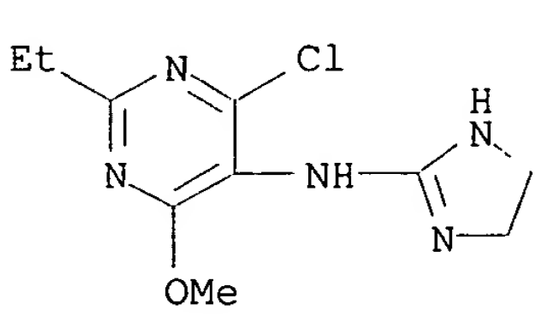
GI



I

AB Antihypertensive (no data) imidazolinylaminopyrimidines I (R-R2 = H, halogen, alkoxy, alkyl; R3 = H, acyl) were prepd. Thus, 5-amino-4,6-dimethoxypyrimidine was treated with NH4NCS and BzCl and the resulting thiourea debenzoylated, s-methylated, and treated with ethylenediamine to give I (R = R2 = OMe, R1 = R3 = H).

L3 ANSWER 25 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 75438-67-4 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2-ethyl-6-methoxy-, hydrochloride (9CI) (CA INDEX NAME)
MF C10 H14 Cl N5 O . x Cl H
LC STN Files: CA, CAPLUS



● x HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 93:239453 Substituted 5-(2-imidazolin-2-yl)-aminopyrimidines. (Beiersdorf A.-G., Fed. Rep. Ger.). Neth. Appl. NL 7908192 19800519, 18 pp. (Dutch). CODEN: NAXXAN. APPLICATION: NL 1979-8192 19791108.

GI

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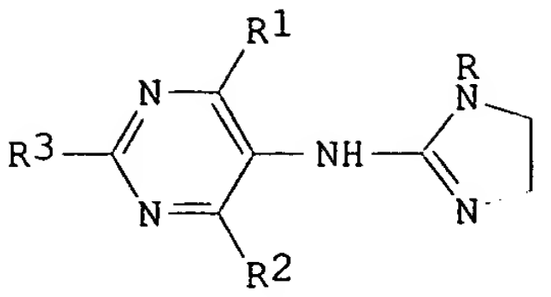
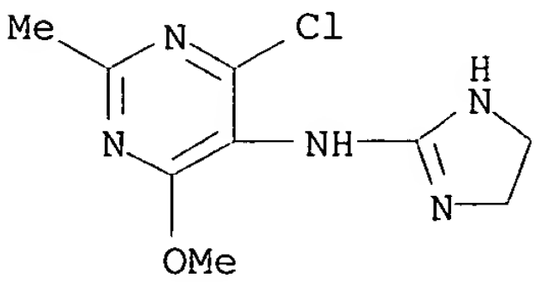


I

AB Imidazolinylaminopyrimidines I (R = H, acyl; R1 - R3 = H, halogen, alkoxy, alkylthio, alkyl, cycloalkyl) were prepd. for use in treating hypertension and glaucoma (no data). Thus 5-amino-4,6-dichloro-2-methylpyrimidine was treated with 1-acetyl-2-imidazolin-2-one to give I (R = Ac, R1 = R2 = Cl, R3 = Me) which was treated with MeSNa to give I (R = H, R1 = SMe, R2 = Cl, R3 = Me). Treatment of the latter compd. with NaOMe gave I (R = H, R1 = SMe, R2 = OMe, R3 = Me).

L3 ANSWER 26 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 75438-58-3 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-, hydrochloride (9CI) (CA INDEX NAME)
MF C9 H12 Cl N5 O . x Cl H
LC STN Files: CA, CAPLUS, IPA, MRCK*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (75438-57-2)



● x HCl

3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:272032 Analgesic composition comprising moxonidine and an opioid analgesic agent. Fairbanks, Carolyn A.; Wilcox, George L.; Stone, Laura S.; Kitto, Kelley F. (Solvay Pharmaceuticals G.m.b.H., Germany). Eur. Pat. Appl. EP 906757 A2 19990407, 8 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1998-117346 19980914. PRIORITY: US 1997-58954 19970916.

AB A pharmaceutical analgesic compn. comprises an opioid analgesic agent and moxonidine as a non-opioid agent with analgesic activity. Administration of an opioid analgesic agent and moxonidine as a non-opioid agent produces analgesia in the treatment of pain in mammals. Synergistic effects of moxonidine and morphine were demonstrated by intrathecal administration to mice; the potency of moxonidine increased 9.2-fold in the presence of morphine and likewise the potency of morphine increased 6.1-fold in the presence of moxonidine. A liq. prepn. for intrathecal aministration

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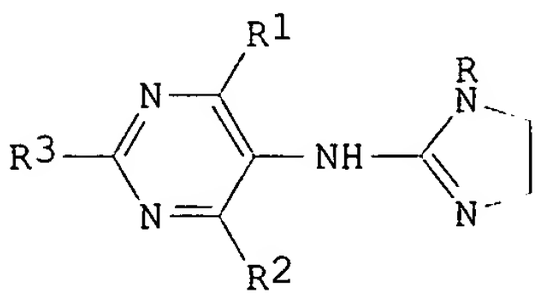
contained morphine sulfate 3.3, moxonidine hydrochloride 0.03, and isotonic aq. saline soln. q.s. to 1 L.

REFERENCE 2: 123:132348 Comparative analysis of effects of imidazoline drugs on isolated rat heart atria. Radwanska, A.; Kaliszan, R. (Dep. Biopharm. Pharmacodyn., Sch. Med., Gdansk, 80416, Pol.). J. Physiol. Pharmacol., 44(1), 73-87 (English) 1993. CODEN: JPHPEI. ISSN: 0867-5910.

AB Effects of cumulative concns. of 16 known imidazoline and 2 imidazole drugs on amplitude and rate of spontaneously beating isolated rat heart atria were measured and related to the resp. effects induced by norepinephrine. In addn., the effects of fixed concns. of the agents on the reponses evoked by cumulative concns. of norepinephrine were detd. In general, imidazolines classified as .alpha.1-adrenoceptor agonists showed pos. inotropic activity providing evidence of involvement of the .alpha.1-adrenoceptor in mediating cardiac contractility. A neg. chronotropic effect was common for the imidazolines studied, including .alpha.1-adrenoceptor agonists, .alpha.2-adrenoceptor agonists, .alpha.1/.alpha.2-adrenoceptor antagonists and antazoline - an antihistaminergic imidazolkine devoid of adrenoceptor affinity. On the other hand, the imidazole deriv., medetomidine, showed a weak pos. chronotropic activity. Neg. chronotropic properties appeared to be independent of the alpha-adrenoceptors and may result from the membrane stabilizing action, involving probably the sodium channel blockage.

REFERENCE 3: 93:239453 Substituted 5-(2-imidazolin-2-yl)-aminopyrimidines. (Beiersdorf A.-G., Fed. Rep. Ger.). Neth. Appl. NL 7908192 19800519, 18 pp. (Dutch). CODEN: NAXXAN. APPLICATION: NL 1979-8192 19791108.

GI



I

AB Imidazolinylaminopyrimidines I (R = H, acyl; R1 - R3 = H, halogen, alkoxy, alkylthio, alkyl, cycloalkyl) were prepd. for use in treating hypertension and glaucoma (no data). Thus 5-amino-4,6-dichloro-2-methylpyrimidine was treated with 1-acetyl-2-imidazolin-2-one to give I (R = Ac, R1 = R2 = Cl, R3 = Me) which was treated with MeSNa to give I (R = H, R1 = SMe, R2 = Cl, R3 = Me). Treatment of the latter compd. with NaOMe gave I (R = H, R1 = SMe, R2 = OMe, R3 = Me).

L3 ANSWER 27 OF 27 REGISTRY COPYRIGHT 2002 ACS
RN 75438-57-2 REGISTRY
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-(6-Chloro-4-methoxy-2-methylpyrimidin-5-ylamino)-2-imidazoline
CN BDF 5895
CN BE 5895
CN Cynt
CN Lomox
CN LY 326869
CN Moxon
CN Moxonidine
CN Norcynt

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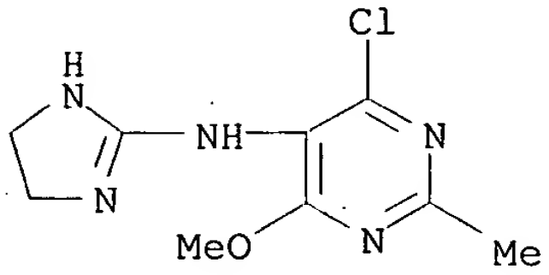
CN Normoxocin
CN Nucynt
CN Physiotens
FS 3D CONCORD
DR 257301-50-1
MF C9 H12 Cl N5 O
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

270 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
270 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:178015 Drugs for incontinence - salified and nonsalified nitric oxide-donors and phosphodiesterase inhibitors. Del Soldato, Piero; Benedini, Francesca (Nicox S.A., Fr.). PCT Int. Appl. WO 2002011707 A2 20020214, 59 pp. DESIGNATED STATES: W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-EP8734 20010727. PRIORITY: IT 2000-MI1848 20000808.

AB Use in the incontinence of one or more of the following classes of drugs selected from the following: (B) salified and nonsalified nitric oxide-donor drugs, of formula: A - X1 - N(O)z, (B') nitrate salts of drugs used for the incontinence, and which do not contain in the mol. a nitric oxide donor group; (C) org. or inorg. salts of compds. inhibiting phosphodiesterases.

REFERENCE 2: 136:177703 Site of action of moxonidine in the rat nephron. Greven, Joachim; von Bronewski-Schwarzer, Brigitte (Department of Pharmacology and Toxicology, Rheinisch-Westfaelische Technische Hochschule Aachen, Aachen, 52057, Germany). Naunyn-Schmiedeberg's Archives of Pharmacology, 364(6), 496-500 (English) 2001. CODEN: NSAPCC. ISSN: 0028-1298. Publisher: Springer-Verlag.

AB Moxonidine is a centrally acting antihypertensive agent which has been found to exert its blood pressure lowering effect by interaction with .alpha.2-adrenoceptors and imidazoline receptors of the I1-type. These receptors have also been demonstrated to be present in the rat kidney. In the present study, clearance and micropuncture techniques were applied to anesthetized rats to localize the site of action of moxonidine within the

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nephron. The clearance data show that moxonidine (0.25 mg/kg i.v., followed by a continuous i.v. infusion of 0.25 mg/h) induced a marked increase in urine flow and urinary excretion of sodium, chloride and potassium. The changes in urine flow and urinary solute excretion were accompanied by an enhanced glomerular filtration rate. The micropuncture expts. revealed that moxonidine significantly increased glomerular filtration rate of superficial nephrons, and significantly inhibited fractional resorption of fluid, sodium, potassium and chloride by similar amts. (by 9.0%-9.8%) in superficial proximal tubules. Regarding fluid and sodium resorption, the proximal effect of moxonidine was continuously weakened by a compensatory increase of resorption in the loop of Henle and the subsequent distal nephron segments. The inhibitory effect of moxonidine on fractional proximal potassium resorption was completely compensated in the loop of Henle, but the drug induced a net secretion of potassium into the segments lying beyond the early distal tubule, probably as a consequence of the increased tubule fluid and sodium load delivered to them. The expts. have identified the proximal tubule as the principal nephron site where the diuretic action of moxonidine arises. The proximal effect may be related to the increased glomerular filtration rate and to a direct inhibitory interaction of moxonidine with the proximal Na+/H+ exchanger.

REFERENCE 3: 136:160718 Moxonidine: clinical profile. Farsang, C. (1st Department of Medicine, St. Imre Teaching Hospital, Budapest, 1115, Hung.). Journal of Clinical and Basic Cardiology, 4(3), 197-200 (English) 2001. CODEN: JCBCFT. ISSN: 1561-2775. Publisher: Krause & Pachernegg GmbH.

AB A review. Several hemodynamic, humoral, and metabolic changes develop in patients with hypertension. Antihypertensive drugs inhibiting or reversing these alterations are of clin. value in the therapy of hypertension. Among these agents, most recently the imidazoline I1 receptor agonists can also be considered as the first therapeutic option. Moxonidine is a selective I1 receptor agonist with a pharmacokinetic profile that enables it to be used once daily. It inhibits the consequences of the increased sympathetic tone, it increases natriuresis, and therefore effectively decreases blood pressure in a wide variety of hypertensive patients. The particular advantage of moxonidine is that it can increase the insulin sensitivity of those patients where it is decreased, therefore it is useful in hypertensive patients with insulin resistance. Moxonidine can be combined with many other antihypertensive drugs such as thiazides, ACE-inhibitors, calcium antagonists, but it can be potentially useful in combinations with alpha1-blockers, angiotensin AT1 blockers, and, in a particular group of patients, with beta-blockers (patients with exaggerated sympathetic tone, or in those with hyperthyroidism).

REFERENCE 4: 136:129363 The I1-imidazoline receptor in PC12 pheochromocytoma cells activates protein kinases C, extracellular signal-regulated kinase (ERK) and c-jun N-terminal kinase (JNK). Edwards, Lincoln; Fishman, Daniel; Horowitz, Peleg; Bourbon, Nicole; Kester, Mark; Ernsberger, Paul (Departments of Nutrition, Medicine, Pharmacology, Case Western Reserve University School of Medicine, Cleveland, OH, 44106-4906, USA). Journal of Neurochemistry, 79(5), 931-940 (English) 2001. CODEN: JONRA9. ISSN: 0022-3042. Publisher: Blackwell Science Ltd..

AB The authors sought to further elucidate signal transduction pathways for the I1-imidazoline receptor in PC12 cells by testing involvement of protein kinase C (PKC) isoforms (.beta., .epsilon., .zeta.), and the mitogen-activated protein kinases (MAPK) ERK and JNK. Stimulation of I1-imidazoline receptor with moxonidine increased enzymic activity of the classical .beta.-isoform in membranes by about 75% and redistributed the atypical isoform into membranes (40% increase in membrane-bound activity), but the novel isoform of PKC was unaffected. Moxonidine and clonidine

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also increased by greater than two-fold the proportion of ERK-1 and ERK-2 in the phosphorylated active form. In addn., JNK enzymic activity was increased by exposure to moxonidine. Activation of ERK and JNK followed similar time courses with peaks at 90 min. The action of moxonidine on ERK activation was blocked by the I1-receptor antagonist efaroxan and by D609, an inhibitor of phosphatidylcholine-selective phospholipase C (PC-PLC), previously implicated as the initial event in I1-receptor signaling. Inhibition or depletion of PKC blocked activation of ERK by moxonidine. Two-day treatment of PC12 cells with the I1/.alpha.2-agonist clonidine increased cell no. by up to 50% in a dose-related manner. These data suggest that ERK and JNK, along with PKC, are signaling components of the I1-receptor pathway, and that this receptor may play a role in cell growth.

REFERENCE 5: 136:123635 Transdermal therapeutic systems with highly dispersed silicon dioxide. Klokkers, Karin; Kramer, Kai-Thomas; Wilhelm, Martina (Hexal A.-G., Germany). PCT Int. Appl. WO 2002003969 A2 20020117, 28 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (German). CODEN: PIXXD2. APPLICATION: WO 2001-EP8070 20010712. PRIORITY: DE 2000-10033853 20000712.

AB The invention relates to a transdermal therapeutic system comprising a surface layer which is impermeable with respect to an active ingredient; a self-adherent matrix layer or a plurality of matrix layers; the matrix layer is self-adherent when the system is applied. The system also comprises a pull-off protective cover; the matrix layer(s) contain(s) one or more active ingredients and/or one or more biol. active substances and highly dispersed silicon dioxide. The system contains silicon dioxide in order to increase skin permeation. Thus a transdermal system contained (w/matrix w%): trandolapril 10; Eutanol G 10; Polyisobutylene adhesive MA24A 76; Aerosil 200 4; after 24 h penetration values of 37.50-58.0 .mu.g/cm2 was measured; the value is higher than for similar transdermal system without silicon dioxide (4.9-14.4 .mu.g/cm2).

REFERENCE 6: 136:91063 Determination of organic residual solvents in moxonidine hydrochloride tablets by GC. Wang, Wei; Gao, Liqin (Tianjin Institute for Drug Control, Tianjin, 300070, Peop. Rep. China). Yaowu Fenxi Zazhi, 21(3), 208-209 (Chinese) 2001. CODEN: YFZADL. ISSN: 0254-1793. Publisher: Yaowu Fenxi Zazhi Bianji Weiyuanhui.

AB The org. residual solvents in moxonidine hydrochloride tablets was detd. by gas chromatog. (GC) on stainless steel column (200 cm x 0.3 cm) with column temp. 118.degree.C. N-Pr alc. was used as the internal std. The linearity was between 100-898 .mu.g mL-1 and 100-904 .mu.g mL-1 with r = 0.9993 and 0.9997 for Et ether and iso-Pr alc., resp. The limit detection was 10 .mu.g mL-1 bor both org. solvents. The recovery was 102.7% and 98.85% with RSD 1.6% and 1.4% for Et ether and iso-Pr alc., resp.

REFERENCE 7: 136:79499 Effects of imidazoline antihypertensive drugs on sympathetic tone and noradrenaline release in the prefrontal cortex. Szabo, Bela; Fritz, Thomas; Wedzony, Krzysztof (Institute of Experimental and Clinical Pharmacology and Toxicology, Albert Ludwigs University, Freiburg i. Br., D-79104, Germany). British Journal of Pharmacology, 134(2), 295-304 (English) 2001. CODEN: BJPCBM. ISSN: 0007-1188. Publisher: Nature Publishing Group.

AB The aim of the present study was to compare the effects of the centrally acting antihypertensive drugs rilmenidine, moxonidine, clonidine and guanabenz on sympathetic tone with their effects on noradrenaline release

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in the cerebral cortex. In particular, the hypothesis was tested that rilmenidine and moxonidine, due to their high affinity for sympatho-inhibitory imidazoline I1 receptors and low affinity for .alpha.2-adrenoceptors, lower sympathetic tone without causing an .alpha.2-adrenoceptor-mediated inhibition of cerebrocortical noradrenaline release. In rats anesthetized with urethane, blood pressure and heart rate were measured and the concn. of noradrenaline in arterial blood plasma was detd. The release of noradrenaline in the medial prefrontal cortex was estd. by microdialysis. I.v. administration of rilmenidine (30, 100, 300 and 1000 .mu.g kg-1), moxonidine (10, 30, 100 and 300 .mu.g kg-1), clonidine (1, 3, 10 and 30 .mu.g kg-1) and guanabenz (1, 3, 10 and 30 .mu.g kg-1) led to dose-dependent hypotension and bradycardia; the plasma noradrenaline concn. also decreased. After the two highest doses, all four drugs lowered noradrenaline release in the prefrontal cortex. At doses eliciting equal hypotensive and sympatho-inhibitory responses, rilmenidine and moxonidine inhibited cerebral cortical noradrenaline release at least as much as clonidine and guanabenz. The results show that rilmenidine and moxonidine lower cerebrocortical noradrenaline release at doses similar to those which cause sympatho-inhibition. This effect was probably due to an .alpha.2-adrenoceptor-mediated inhibition of the firing of locus coeruleus neurons and, in addn., to presynaptic inhibition of noradrenaline release at the level of the axon terminals in the cortex. The results argue against the hypothesis that rilmenidine and moxonidine, due to their selectivity for sympatho-inhibitory I1 imidazoline receptors, do not suppress noradrenergic neurons in the central nervous system.

REFERENCE 8: 136:58848 Curative method for pathologic syndromes and homeopathic medicinal preparations. Epshtein, Oleg Iliich; Kolyadko, Tamara Mikhailovna; Shtark, Mark Borisovich (Russia). PCT Int. Appl. WO 2001097842 A1 20011227, 100 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (Russian). CODEN: PIXXD2. APPLICATION: WO 2001-RU239 20010619. PRIORITY: RU 2000-115594 20000620.

AB The inventive curative method for a pathol. syndrome consists in inserting into an organism activated forms of minute antibody doses which are produced by means of a repeated successive diln. and an external action carried out on an antigen, e.g. a substance or medicinal prepn. influencing a mechanism forming said pathol. syndrome. The inventive medicinal prepn. for curing the pathol. syndrome comprises an activated form of minute doses of monoclonal, polyclonal or natural antibodies. Said antibodies are produced by means of a repeated successive diln. and an external action, preferably using homeopathic technol., which is carried out on an antigen, e.g. a substance or medicinal prepn. directly promoting the formation of the pathol. syndrome or participating in regulating mechanisms for the formation thereof. Activated forms of minute doses of antibodies to the antigens of an exogenic and endogenic nature, autoantigens and fetal antigens, are used. Anti-idiotypic antibodies are also used.

REFERENCE 9: 136:58646 Determination of ionization constant and partition coefficient of moxonidine. Zhang, Yuanxing; Wu, Fenglan; Li, Yuzhen (Department of Pharmacy, People's Hospital, Beijing University, Beijing, 100083, Peop. Rep. China). Shenyang Yaoke Daxue Xuebao, 18(1), 37-39 (Chinese) 2001. CODEN: SYDXFF. ISSN: 1006-2858. Publisher: Shenyang Yaoke Daxue Xuebao Bianjibu.

AB The methods for detg. the ionization const. and partition coeff. of

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moxonidine were presented. The ionization const. was detd. by potential titrn. method, and pKaT was 7.35.+-.0.03. The partition coeff. was detd. by bottle-shaking method, and P was 12.02.+-.0.13.

REFERENCE 10: 136:48245 ACE-depended and sympathetic components of arterial blood pressure regulation in patients with essential hypertension. Aparina, T. V.; Gomazkov, O. A.; Dilakyan, E. A.; Britov, A. N. (Gos. NII Tsentr Profilakticheskoi Kardiol., MZ RF, Russia). Voprosy Meditsinskoi Khimii, 47(4), 411-418 (Russian) 2001. CODEN: VMDKAM. ISSN: 0042-8809. Publisher: NII Biomeditsinskoi Khimii.

AB The development of arterial hypertension is accompanied by impairment of the normal ratio of the sympathetic and humoral "ACE-depending" parts of regulation of the arterial pressure. The main targets of antihypertensive agents are imidazoline receptors and particularly ACE, the main component of angiotensin-renin system. The aim of the present investigation was to det. the hypotensive and metabolic effects of moxonidine, imidazoline receptor agonist, and enalapril, ACE inhibitor, depending on the basal ACE activity in patients with essential hypertension. Effectiveness of moxonidine and enalapril administration (diring 24 wk) depended on the basal ACE activity in the hypertensive patients: (a) in the group of patients with low basal ACE activity moxonidine very effectively decreased systolic and diastolic blood pressure, compared with the group of patients with high basal ACE activity; (b) influence of enalapril on the level of arterial blood pressure was more pronounced with high basal ACE activity. In conclusion: choosing a hypotensive treatment for patients with the metabolic syndrome, it is advisable to take into account the basal ACE activity levels.

```
=> e
"4-chloro-5-((4,5-dihydro-1h-imidazol-2-yl)-amino)-6-methoxy-2-methylpyrimidine"/cn
5
E1            1      4-CHLORO-5,8-DIMETHYLQUINOLINE-3-CARBOXYLIC ACID/CN
E2            1      4-CHLORO-5-((2-METHYL-4-NITROPHENYL)IMINO)-5H-1,2,3-DITHIAZO
                     LE/CN
E3            0 --> 4-CHLORO-5-((4,5-DIHYDRO-1H-IMIDAZOL-2-YL)-AMINO)-6-METHOXY-
                     2-METHYLPYRIMIDINE/CN
E4            1      4-CHLORO-5-((ETHOXYCARBONYL)OXY)-2-FLUOROANILINE/CN
E5            1      4-CHLORO-5-(2,3-DICHLOROPHENOXY)-2-NITROANILINE/CN

=> s chloro(l)dihydro(l)imidazol?(l)amino(l)methoxy(l)methyl(l)pyrimidine
       2779352 CHLORO
            43 CHLOROS
       2779352 CHLORO
                  (CHLORO OR CHLOROS)
       1911928 DIHYDRO
            55 DIHYDROS
       1911928 DIHYDRO
                  (DIHYDRO OR DIHYDROS)
        561788 IMIDAZOL?
       3598461 AMINO
          8552 AMINOS
       3598461 AMINO
                  (AMINO OR AMINOS)
       2776425 METHOXY
      11117684 METHYL
            93 METHYLS
      11117684 METHYL
                  (METHYL OR METHYLS)
        271696 PYRIMIDINE
             1 PYRIMIDINES
        271696 PYRIMIDINE
```

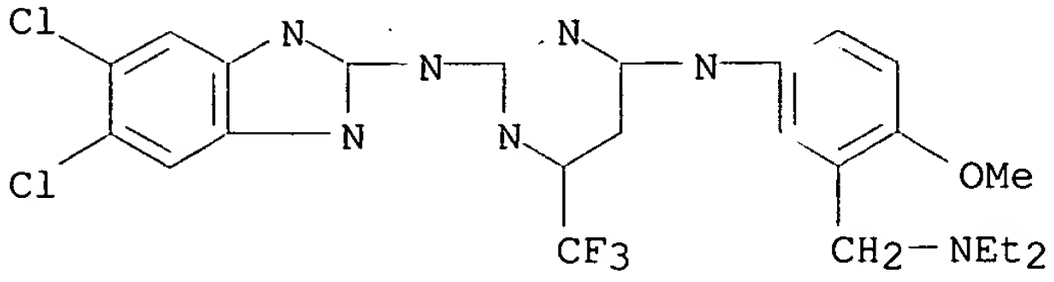
Searched by: Mary Hale 308-4258 CM-1 12D16

(PYRIMIDINE OR PYRIMIDINES)
L4 3 CHLORO(L)DIHYDRO(L)IMIDAZOL?(L)AMINO(L)METHOXY(L)METHYL(L)PYRIMI
DINE

=> s l4 not l3
L5 3 L4 NOT L3

=> d 1-3 ide cbib abs

L5 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 86260-60-8 REGISTRY
CN **2,4-Pyrimidinediamine, N2-(5,6-dichloro-1H-benzimidazol-2-yl)-N4-[3-[(diethylamino)methyl]-4-methoxyphenyl]-6-(trifluoromethyl)-, dihydrochloride (9CI)** (CA INDEX NAME)
MF C24 H24 Cl2 F3 N7 O . 2 Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)

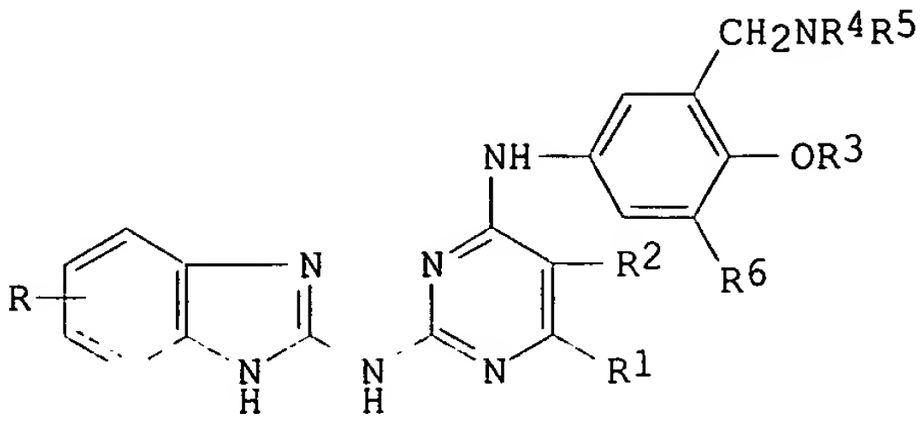



●2 HCl

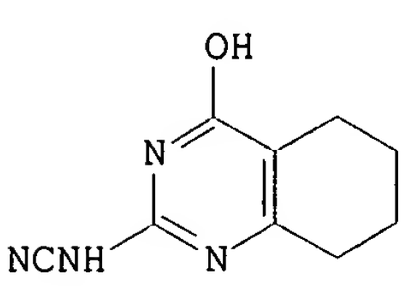
*** FRAGMENT DIAGRAM IS INCOMPLETE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 99:88150 N2-1H-Benzimidazol-2-yl-N4-phenyl-2,4-pyrimidinediamines and N2-1H-benzimidazol-2-yl-5,6,7,8-tetrahydro-N4-phenyl-2,4-quinazolinediamines as potential antifilarial agents. Angelo, Mario M.; Ortwine, Daniel; Worth, Donald F.; Werbel, Leslie M. (Warner-Lambert/Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Ann Arbor, MI, 48106, USA). J. Med. Chem., 26(9), 1311-16 (English) 1983. CODEN: JMCMAR. ISSN: 0022-2623.
GI

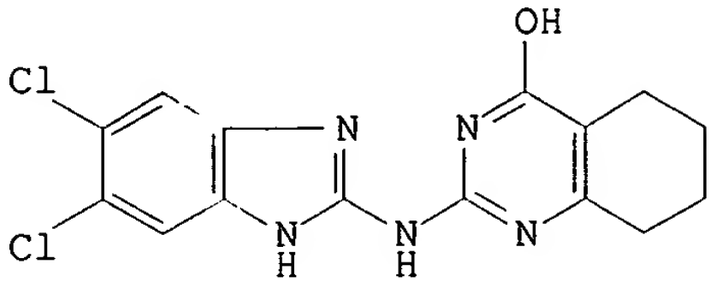
Searched by: Mary Hale 308-4258 CM-1 12D16



I



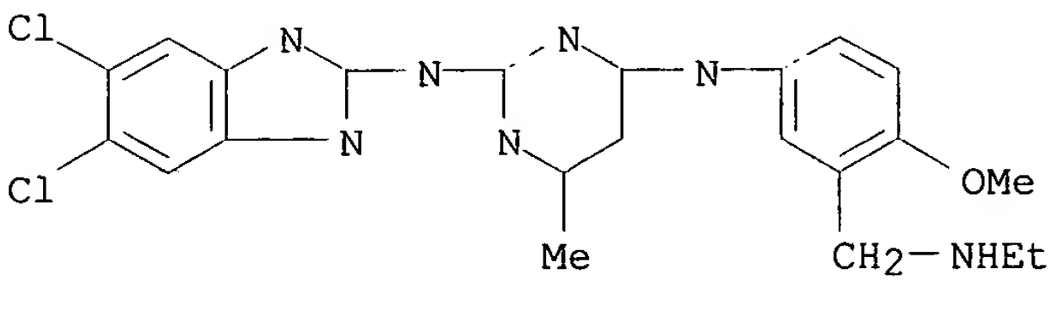
II



III

AB Title compds. I [R = 5,6-Cl2, 5-Bz; R1 = Me, CF3, Ph; R2 = H; R1R2 = (CH2)4; R3 = H, Me, Et; NR4R5 = NEt2, pyrrolidino, NHEt, 4-methylpiperazinyl, PhNEt; R6 = H, Ph] were prepd., but showed no antifilarial activity. Thus, treating cyanamide II with 2,4,5-H2NCl2C6H2NH2 gave benzimidazole III, whose chlorination followed by amination with 2,5-HO(NH2)C6H3CH2NEt2 gave I (R = 5,6-Cl2, R1R2 = (CH2)4, R3 = R6 = H, NR4R5 = NEt2).

L5 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 86260-58-4 REGISTRY
CN **2,4-Pyrimidinediamine, N2-(5,6-dichloro-1H-benzimidazol-2-yl)-N4-[3-[(ethylamino)methyl]-4-methoxyphenyl]-6-methyl-, dihydrochloride (9CI)** (CA INDEX NAME)
MF C22 H23 Cl2 N7 O . 2 Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)



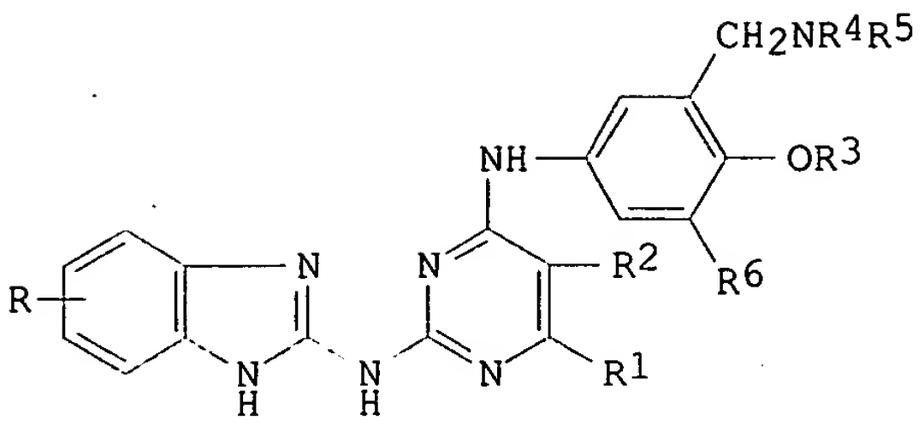
●2 HCl

*** FRAGMENT DIAGRAM IS INCOMPLETE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 99:88150 N2-1H-Benzimidazol-2-yl-N4-phenyl-2,4-pyrimidinediamines and N2-1H-benzimidazol-2-yl-5,6,7,8-tetrahydro-N4-phenyl-2,4-quinazolinediamines as potential antifilarial agents. Angelo, Mario M.; Ortwine, Daniel; Worth, Donald F.; Werbel, Leslie M. (Warner-Lambert/Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Ann Arbor, MI, 48106, USA). J. Med. Chem., 26(9), 1311-16 (English) 1983. CODEN: JMCMAR. ISSN: 0022-2623.

Searched by: Mary Hale 308-4258 CM-1 12D16

GI



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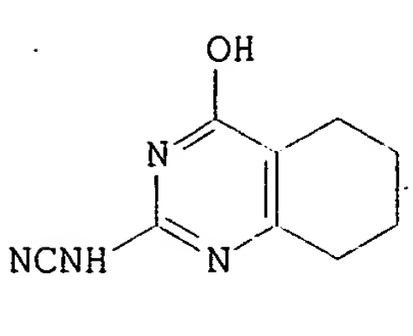
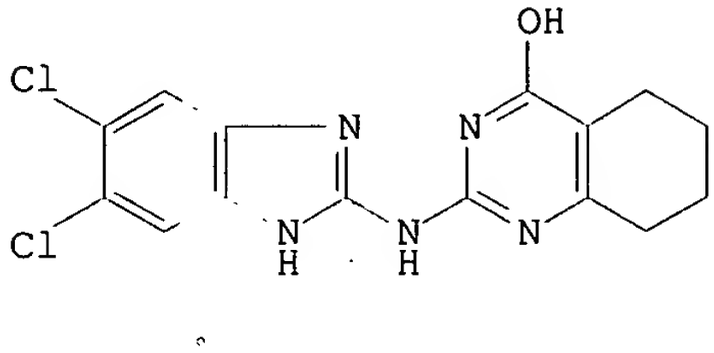


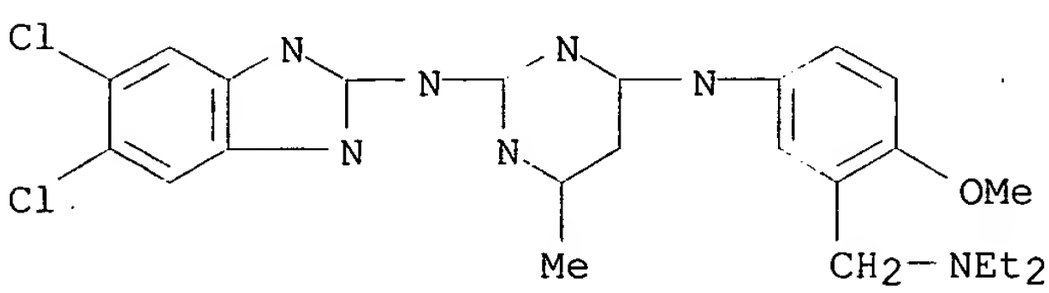
II



III

AB Title compds. I [R = 5,6-Cl2, 5-Bz; R1 = Me, CF3, Ph; R2 = H; R1R2 = (CH2)4; R3 = H, Me, Et; NR4R5 = NEt2, pyrrolidino, NHEt, 4-methylpiperazinyl, PhNEt; R6 = H, Ph] were prepd., but showed no antifilarial activity. Thus, treating cyanamide II with 2,4,5-H2NCl2C6H2NH2 gave benzimidazole III, whose chlorination followed by amination with 2,5-HO(NH2)C6H3CH2NEt2 gave I (R = 5,6-Cl2, R1R2 = (CH2)4, R3 = R6 = H, NR4R5 = NEt2).

L5 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN 86260-55-1 REGISTRY
CN **2,4-Pyrimidinediamine, N2-(5,6-dichloro-1H-benzimidazol-2-yl)-N4-[3-[(diethylamino)methyl]-4-methoxyphenyl]-6-methyl-, dihydrochloride (9CI)** (CA INDEX NAME)
MF C24 H27 Cl2 N7 O . 2 Cl H
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)
CRN (42389-11-7)



●2 HCl

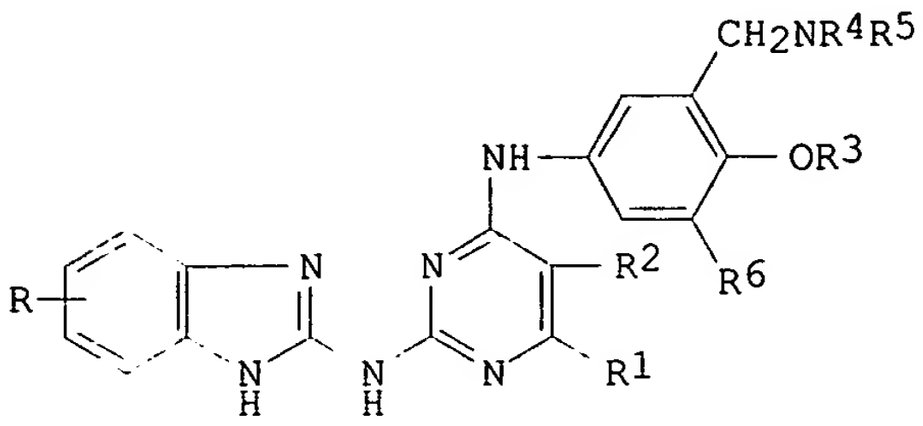
*** FRAGMENT DIAGRAM IS INCOMPLETE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 99:88150 N2-1H-Benzimidazol-2-yl-N4-phenyl-2,4-pyrimidinediamines and N2-1H-benzimidazol-2-yl-5,6,7,8-tetrahydro-N4-phenyl-2,4-quinazolinediamines as potential antifilarial agents. Angelo, Mario M.; Ortwine, Daniel; Worth, Donald F.; Werbel, Leslie M.

Searched by: Mary Hale 308-4258 CM-1 12D16

(Warner-Lambert/Parke-Davis Pharm. Res. Div., Warner-Lambert Co., Ann Arbor, MI, 48106, USA). J. Med. Chem., 26(9), 1311-16 (English) 1983. CODEN: JMCMAR. ISSN: 0022-2623.

GI



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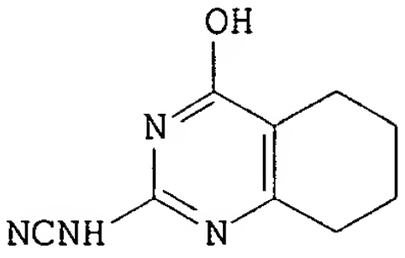
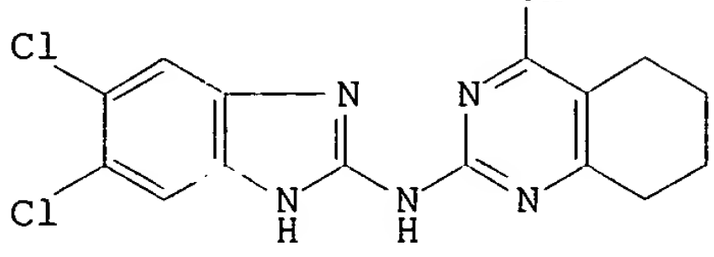


II



III

AB Title compds. I [R = 5,6-Cl2, 5-Bz; R1 = Me, CF3, Ph; R2 = H; R1R2 = (CH2)4; R3 = H, Me, Et; NR4R5 = NEt2, pyrrolidino, NHEt, 4-methylpiperazinyl, PhNEt; R6 = H, Ph] were prepd., but showed no antifilarial activity. Thus, treating cyanamide II with 2,4,5-H2NCl2C6H2NH2 gave benzimidazole III, whose chlorination followed by amination with 2,5-HO(NH2)C6H3CH2NEt2 gave I (R = 5,6-Cl2, R1R2 = (CH2)4, R3 = R6 = H, NR4R5 = NEt2).

=> fil medl,caplus,biosis,embase,wpids,jicst

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 283.36 | 283.57 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -17.70 | -17.70 |

FILE 'MEDLINE' ENTERED AT 15:07:16 ON 02 APR 2002

FILE 'CAPLUS' ENTERED AT 15:07:16 ON 02 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE 'BIOSIS' ENTERED AT 15:07:16 ON 02 APR 2002


FILE 'EMBASE' ENTERED AT 15:07:16 ON 02 APR 2002


FILE 'WPIDS' ENTERED AT 15:07:16 ON 02 APR 2002


FILE 'JICST-EPLUS' ENTERED AT 15:07:16 ON 02 APR 2002


Searched by: Mary Hale 308-4258 CM-1 12D16

```
=> s l3 or chloro(l)dihydro(l)imidazol?(l)amino(l)methoxy(l)(methylpyrimidine or
methyl pyrimidine)
L6            228 FILE MEDLINE
L7            274 FILE CAPLUS
L8            364 FILE BIOSIS
L9            673 FILE EMBASE
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by
structure-building or screen commands and text search terms.  L#s
created via the STRUCTURE or SCREEN commands must be searched in the
structures files separately from text terms or profiles.  The L#
answer sets from structure searches can be used in crossover searches
and can be combined with text terms.

=> s (l3 or chloro(l)dihydro(l)imidazol?(l)amino(l)methoxy(l)(methylpyrimidine or
methyl pyrimidine))
L10           228 FILE MEDLINE
L11           274 FILE CAPLUS
L12           364 FILE BIOSIS
L13           673 FILE EMBASE
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by
structure-building or screen commands and text search terms.  L#s
created via the STRUCTURE or SCREEN commands must be searched in the
structures files separately from text terms or profiles.  The L#
answer sets from structure searches can be used in crossover searches
and can be combined with text terms.

=> fil medl,caplus,embase,biosis,wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    35.83     319.40

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -17.70

FILE 'MEDLINE' ENTERED AT 15:09:47 ON 02 APR 2002

FILE 'CAPLUS' ENTERED AT 15:09:47 ON 02 APR 2002
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FILE 'EMBASE' ENTERED AT 15:09:47 ON 02 APR 2002
COPYRIGHT (C) 2002 Elsevier Science B.V.  All rights reserved.

FILE 'BIOSIS' ENTERED AT 15:09:47 ON 02 APR 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'WPIDS' ENTERED AT 15:09:47 ON 02 APR 2002
COPYRIGHT (C) 2002 DERWENT INFORMATION LTD

=> s (l3 or chloro(l)dihydro(l)imidazol?(l)amino(l)methoxy(l)(methylpyrimidine or
methyl pyrimidine))
L14           228 FILE MEDLINE
L15           274 FILE CAPLUS
L16           673 FILE EMBASE
L17           364 FILE BIOSIS
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by
structure-building or screen commands and text search terms.  L#s


Searched by: Mary Hale 308-4258 CM-1 12D16
```

created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

```
=> s (chloro(l)dihydro(l)imidazol?(l)amino(l)methoxy(l)(methylpyrimidine or methyl
pyrimidine))
L18             0 FILE MEDLINE
L19             0 FILE CAPLUS
L20             0 FILE EMBASE
L21             0 FILE BIOSIS
L22             5 FILE WPIDS

TOTAL FOR ALL FILES
L23             5 (CHLORO(L) DIHYDRO(L) IMIDAZOL?(L) AMINO(L) METHOXY(L)(METHYLPYR
                  IMIDINE OR METHYL PYRIMIDINE))

=> fil reg;e moxonidine/cn 5
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                       33.70     353.10

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                          ENTRY    SESSION
CA SUBSCRIBER PRICE                                        0.00     -17.70

FILE 'REGISTRY' ENTERED AT 15:10:43 ON 02 APR 2002
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STRUCTURE FILE UPDATES:   31 MAR 2002  HIGHEST RN 403694-27-9
DICTIONARY FILE UPDATES:  31 MAR 2002  HIGHEST RN 403694-27-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the
CAS Registry Numbers that were added to the H/Z/CA/CAplus files between
12/27/01 and 1/23/02.  Use of the P indicator in online and SDI searches
during this period, either directly appended to a CAS Registry Number
or by qualifying an L-number with /P, may have yielded incomplete results.
As of 1/23/02, the situation has been resolved.  Also, note that searches
conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files
incorporating CAS Registry Numbers with the P indicator between 12/27/01
and 1/23/02, are encouraged to re-run these strategies.  Contact the
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,
worldwide, or send an e-mail to help@cas.org for further assistance or to
receive a credit for any duplicate searches.


Searched by: Mary Hale 308-4258 CM-1 12D16
```

```
E1            1      MOXNIDAZOLE/CN
E2            1      MOXON/CN
E3            1  --> MOXONIDINE/CN
E4            1      MOXR (MYCOBACTERIUM LEPRAE STRAIN TN GENE MOXR)/CN
E5            1      MOXR PROTEIN (CAULOBACTER CRESCENTUS GENE CC0566)/CN

=> s e3;d ide can
L24           1 MOXONIDINE/CN


L24  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   75438-57-2  REGISTRY
CN   5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-
     methyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   2-(6-Chloro-4-methoxy-2-methylpyrimidin-5-ylamino)-2-imidazoline
CN   BDF 5895
CN   BE 5895
CN   Cynt
CN   Lomox
CN   LY 326869
CN   Moxon
CN   Moxonidine
CN   Norcynt
CN   Normoxocin
CN   Nucynt
CN   Physiotens
FS   3D CONCORD
DR   257301-50-1
MF   C9 H12 Cl N5 O
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CIN, DDFU, DRUGNL, DRUGPAT,
       DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*,
       SYNTHLINE, TOXCENTER, USAN, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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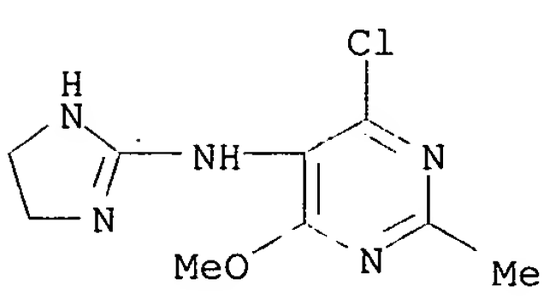


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

          270 REFERENCES IN FILE CA (1967 TO DATE)
            3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
          270 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE   1:  136:178015

REFERENCE   2:  136:177703

REFERENCE   3:  136:160718

Searched by: Mary Hale 308-4258 CM-1 12D16
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REFERENCE  4:  136:129363

REFERENCE  5:  136:123635

REFERENCE  6:  136:91063

REFERENCE  7:  136:79499

REFERENCE  8:  136:58848

REFERENCE  9:  136:58646

REFERENCE 10:  136:48245

=> fil medl,caplus,biosis,embase,wpids,jicst

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 6.16 | 359.26 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | 0.00 | -17.70 |

FILE 'MEDLINE' ENTERED AT 15:11:26 ON 02 APR 2002

FILE 'CAPLUS' ENTERED AT 15:11:26 ON 02 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE 'BIOSIS' ENTERED AT 15:11:26 ON 02 APR 2002


FILE 'EMBASE' ENTERED AT 15:11:26 ON 02 APR 2002


FILE 'WPIDS' ENTERED AT 15:11:26 ON 02 APR 2002


FILE 'JICST-EPLUS' ENTERED AT 15:11:26 ON 02 APR 2002


=> s (13 or moxonidine or 75438-57-2 or norcynt or nucynt or moxon or cynt)
L25  334 FILE MEDLINE
L26  433 FILE CAPLUS
L27  439 FILE BIOSIS
L28  710 FILE EMBASE
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by
structure-building or screen commands and text search terms.  L#s
created via the STRUCTURE or SCREEN commands must be searched in the
structures files separately from text terms or profiles.  The L#
answer sets from structure searches can be used in crossover searches
and can be combined with text terms.

=> s l3
L29  228 FILE MEDLINE
L30  274 FILE CAPLUS
L31  364 FILE BIOSIS
L32  673 FILE EMBASE

Searched by: Mary Hale 308-4258 CM-1 12D16

```
FILE 'WPIDS'
SAMPLE SEARCH INITIATED 15:12:18
SAMPLE SCREEN SEARCH COMPLETED -      0 TO ITERATE

100.0% PROCESSED       0 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             0 TO         0
PROJECTED ANSWERS:                0 TO         0

L33            0 SEA SSS SAM L1
L34          0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L35       1539 L3

=> s ( moxonidine or 75438-57-2 or norcynt or nucynt or moxon or cynt)
L36        334 FILE MEDLINE
L37        431 FILE CAPLUS
L38        439 FILE BIOSIS
L39        710 FILE EMBASE
L40         22 FILE WPIDS
L41          3 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L42       1939 (MOXONIDINE OR 75438-57-2 OR NORCYNT OR NUCYNT OR MOXON OR CYNT)


=> s (l35 or l42) and (myocard?(2a)(infarc? or damag? or heart fail? or
hypertroph?)
UNMATCHED LEFT PARENTHESIS 'AND (MYOCARD?'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s (l35 or l42) and (myocard?(2a)(infarc? or damag? or heart fail? or
hypertroph?))
L43          7 FILE MEDLINE
L44          5 FILE CAPLUS
L45          9 FILE BIOSIS
L46         12 FILE EMBASE
L47          2 FILE WPIDS
L48          0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L49         35 (L35 OR L42) AND (MYOCARD?(2A)(INFARC? OR DAMAG? OR HEART FAIL?
               OR HYPERTROPH?))

=> dup rem l49
PROCESSING COMPLETED FOR L49
L50          19 DUP REM L49 (16 DUPLICATES REMOVED)

=> d 1-19 cbib abs hitstr;s (l35 or l42) and (post myocardia? or ischemic myocardi?
or heart muscle necrosis or thrombolytic or fibrinolytic therap? or reperfus> or
sympathetic nervous system or heart fail? or cardia hypertroph?)

L50  ANSWER 1 OF 19  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:394222  Document No.: PREV200100394222. Prevention of hypertrophy improves
     capillay density and ischemic tolerance in rat hearts. Van Kerckhoven,
     Roeland (1); Saxena, Pramod R. (1); Schoemaker, Regien G. (1). (1) Dept of

Searched by: Mary Hale 308-4258 CM-1 12D16
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Pharmacology, Erasmus University, Rotterdam Netherlands. Journal of Molecular and Cellular Cardiology, (June, 2001) Vol. 33, No. 6, pp. A179. print. Meeting Info.: XVII ISHR World Congress of the International Society for Heart Research Banff, Alberta, Canada July 02-05, 2001 ISSN: 0022-2828. Language: English. Summary Language: English.

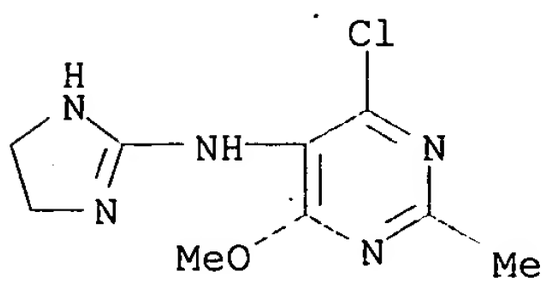
L50 ANSWER 2 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:437507 Document No.: PREV200100437507. Prevention of hypertrophy improves capillary density and ischemic tolerance in rat hearts. Van Kerckhoven, Roeland (1); Saxena, Pramod R. (1); Schoemaker, Regien G. (1). (1) Dept of Pharmacology, Erasmus University, Rotterdam Netherlands. Journal of Molecular and Cellular Cardiology, (June, 2001) Vol. 33, No. 6, pp. A58. print. Meeting Info.: XVII ISHR World Congress of the International Society for Heart Research Winnipeg, Canada July 06-11, 2001 ISSN: 0022-2828. Language: English. Summary Language: English.

L50 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
2000:741923 Document No. 133:291116 Method and means for preventing, treating, and diagnosing cardiovascular complications in patients with obstructive sleep apnea. Hedner, Jan; Grote, Ludger (Swed.). PCT Int. Appl. WO 2000061144 A1 20001019, 16 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-SE688 20000411. PRIORITY: SE 1999-1295 19990413.

AB A method of preventing and/or treating sympathetically induced cardiovascular complications such as coronary artery disease, cardiac failure, **myocardial infarction**, and stroke, in patients with obstructive sleep apnea (OSA) disorder, comprises inhibiting the activation of the sympathoadrenergic system by administration of a pharmacol. effective amt. of an I1-receptor agonist (IRA) prior to and/or during a period of sleep. Also disclosed is the use of an I1-imidazoline receptor agonist (IRA) for the diagnosis of such complications and for the manuf. of a medicament for preventing and/or treating sympathetically induced cardiovascular complications during sleep in patients with a sleep related breathing disorder.

IT **75438-57-2, Moxonidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method and means for preventing, treating, and diagnosing cardiovascular complications in patients with obstructive sleep apnea)

RN 75438-57-2 CAPLUS
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)




L50 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2

Searched by: Mary Hale 308-4258 CM-1 12D16

Same as Appln Prior.

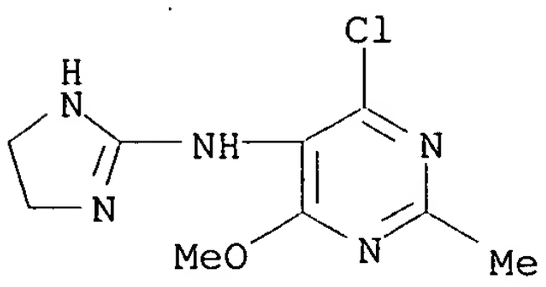
2000:533370 Document No. 133:115126 **Moxonidine** for treatment after cardiac infarct. Schoemaker, Regina Geertruida (Solvay Pharmaceuticals G.m.b.H., Germany). Ger. Offen. DE 10003771 A1 20000803, 8 pp. (German). CODEN: GWXXBX. APPLICATION: DE 2000-10003771 20000128. PRIORITY: DE 1999-19903780 19990201.

AB **Moxonidine** and its physiol. compatible acid addn. salts are useful for treatment of **myocardial damage** resulting from cardiac infarct and prevention of progression of cardiac weakness after **myocardial infarction**. Thus, rats were subjected to coronary artery ligation and treated with **moxonidine** (3 or 6 mg/kg/day s.c.) beginning 24 h later and continuing for 3 wk. The **moxonidine** treatment prevented cardiac hypertrophy, tachycardia, increased levels of plasma noradrenaline, and (at 6 mg/kg/day) increased levels of interstitial collagen in the heart which were seen in untreated rats with infarcts. Tablets were prepd. contg. **moxonidine** 0.025, lactose 9.575, povidone 0.070, crospovidone 0.300, Mg stearate 0.030, and H2O 0.750 parts. These tablets 10.000 were coated with a film comprising hydroxypropylmethylcellulose 0.156, 30% aq. ethylcellulose dispersion 0.480, PEG-6000 0.030, TiO2 0.150, talc 0.1197, red Fe oxide 0.0003, and H2O 3.864 parts and dried at 45.degree..

IT **75438-57-2, Moxonidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**moxonidine** for treatment after cardiac infarct)

RN 75438-57-2 CAPLUS

CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)




L50 ANSWER 5 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001019343 EMBASE MCI-154: A second generation Ca(2+) sensitizer that does not impair relaxation - A novel approach to the treatment of heart failure. Kitada Y.. Dr. Y. Kitada, Pharmaceut. Research Laboratory II, Research Center, Mitsubishi-Tokyo Pharmaceut. Inc., 1000 Kamoshida-cho, Aoba-ku, Yokohama 227-0033, Japan. Cardiovascular Drug Reviews 18/4 (271-283) 2000.
Refs: 57.
ISSN: 0897-5957. CODEN: CDREEA. Pub. Country: United States. Language: English. Summary Language: English.

AB With the negative results of the cyclic AMP-dependent positive inotropic agents in clinical trials, great interest has been focused on the development of agents that directly activate cardiac myofilaments. These drugs are called "Ca(2+) sensitizers"; they are expected to represent a possible new pharmacological approach to the therapy of chronic heart failure. MCI-154 is one of the most powerful and promising Ca(2+) sensitizers currently in clinical trials. In preclinical studies, the positive inotropic action of MCI-154 was observed at the concentrations at which the drug did not increase intracellular Ca(2+). In skinned cardiac muscle fiber bundles from various animal species MCI-154 shifted P(Ca) (-log [Ca(2+)] M)-force relation upward and to the left, suggesting that this drug not only increases sensitivity of myofibrils to Ca(2+), but also enhances cross-bridge interaction. In regard to the molecular mechanism of

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action of MCI-154, the earliest experiments showed that MCI-154 at the high concentration (10(-4) M) stimulated binding of Ca(2+) to troponin (Tn) C. However, MCI-154-(at concentrations lower than 10(-5) M)-induced increase in the affinity of TnC to Ca(2+) led to the complex formation of TnC with Tnl and TnT. This effect of the drug on Ca(2+) regulation and interaction between troponin subunits was discovered using fluorescence spectroscopy. At 10(-4) M MCI-154 decreased binding of Ca(2+) to TnC. The Ca(2+) sensitizing effect of MCI-154 disappeared when cardiac Tnl was exchanged for skeletal Tnl. Taken together, it can be concluded that Tnl may represent a target protein for the positive inotropic action of MCI-154. The long-term treatment with MCI-154 prolonged the life span of cardiomyopathic hamsters, Biol4.6, a model that resembles human heart failure. Unlike PDE inhibitors, MCI-154 did not aggravate arrhythmias generated in the two-stage coronary ligation-, digitalis- and catecholamine-induced canine arrhythmia models. In clinical studies MCI-154 improved contractile function in patients with left ventricular dysfunction after **myocardial infarction**. Its effect was not associated with an increase in myocardial oxygen consumption or impaired relaxation. In conclusion, MCI-154 could be promising in the treatment of chronic heart failure. Clinical studies with MCI-154 are currently in progress.

L50 ANSWER 6 OF 19 MEDLINE DUPLICATE 3

2000411996 Document Number: 20304640. PubMed ID: 10844105. Chronic administration of **moxonidine** suppresses sympathetic activation in a rat heart failure model. Van Kerckhoven R; van Veen T A; Boomsma F; Saxena P R; Schoemaker R G. (Department of Pharmacology, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR, Rotterdam, Netherlands.. vankerckhoven@farma.fgg.eur.nl) . EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 May 26) 397 (1) 113-20. Journal code: EN6; 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB Excessive sympathetic activity contributes to cardiovascular abnormalities, which negatively affect the prognosis of heart failure. The present study evaluated the effects of **moxonidine**, an imidazoline I(1) receptor agonist, on sympathetic activation and myocardial remodelling in a rat heart failure model. Rats were subjected to coronary artery ligation, and treated with **moxonidine**, 3 or 6 mg/kg/day, from 1 to 21 days after **myocardial infarction** . After 21 days, heart rate and blood pressure were measured in conscious, chronically instrumented rats. Plasma catecholamine levels were determined by high-performance liquid chromatography. Effects on post-**myocardial infarction** remodelling were evaluated from the ventricular weight body weight ratio and interstitial collagen deposition, measured morphometrically in the interventricular septum remote from the infarcted area. **Moxonidine** dose-dependently decreased **myocardial infarction** induced tachycardia but did not affect **myocardial infarction** reduced blood pressure. Plasma noradrenaline levels, which were elevated after **myocardial infarction**, decreased below sham-values with 6 mg/kg/day **moxonidine**. Ventricular weight-body weight ratio as well as interstitial collagen were significantly elevated in **myocardial infarcted** rats, and restored to sham values with 6 mg/kg/day **moxonidine**. These data suggest that **moxonidine** suppresses **myocardial infarction** induced sympathetic activation in a dose-dependent way as indicated by reduced heart rate and plasma noradrenaline levels. Furthermore, post-**myocardial infarction** remodelling may be attenuated at a higher dose-range of **moxonidine** as shown by normalisation of ventricular weight body weight ratio and interstitial collagen.

L50 ANSWER 7 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

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2000020521 EMBASE [The importance of the imidazolin-I1 receptor agonists in the treatment of hypertension]. AZ IMIDAZOLIN-1-RECEPTOR-AGONISTAK JELENTOSEGE A HYPERTONIA KEZELESEBEN. Kapocsi J.. Dr. J. Kapocsi, I Belogyogyaszati Osztaly, Szent Imre Korhaz, Tetenyi ut 12-15, 1115 Budapest, Hungary. Lege Artis Medicine 9/12 (943-948) 1999.
Refs: 34.
ISSN: 0866-4811. CODEN: LAMEFU. Pub. Country: Hungary. Language: Hungarian. Summary Language: English; Hungarian.

AB The hypothesis and indirect evidence of imidazoline receptors has been promoted since some 15 years ago and it gave a substantial impetus for research in this field, resulting in a better understanding of neuronal and cardiovascular regulatory processes. There are numerous data, that clonidine, rilmenidine and **moxonidine** (centrally acting antihypertensive agents) have agonistic activity on the imidazolin-1 receptors, resulting in a decrease of sympathetic outflow from the central nervous system. It is generally accepted, that sympathetic neuronal activity plays a key role not only in the cardiovascular and metabolic homeostatic control, but also in the pathogenesis and/or in the progression of several cardiovascular and metabolic diseases (essential hypertension, **myocardial infarction**, cardiac arrhythmias, congestive heart failure, atherosclerosis, hyperlipidemia, decreased glucose tolerance). High blood pressure is frequently associated with these cardiovascular and metabolic alterations. The goal of a properly individualized antihypertensive treatment is not only to decrease blood pressure but to prevent and/or reverse the target organ damages and metabolic alterations. Concerning the results, originating from the research and clinical investigations of the imidazolin-1 receptor agonists, these agents are promising new tools in the treatment of hypertension.

L50 ANSWER 8 OF 19 MEDLINE DUPLICATE 4
2000324366 Document Number: 20324366. PubMed ID: 10868514. Sympathetic activation and the role of beta-blockers in chronic heart failure. Krum H. (Clinical Pharmacology Unit, Monash University, Alfred Hospital, Melbourne, Vic. ) AUSTRALIAN AND NEW ZEALAND JOURNAL OF MEDICINE, (1999 Jun) 29 (3) 418-27. Ref: 45. Journal code: 9H9; 1264322. ISSN: 0004-8291. Pub. country: Australia. Language: English.

AB Chronic heart failure (CHF) is associated with activation of the sympathetic nervous system. This activation provides short term haemodynamic support to the failing myocardium, but may be deleterious over longer periods as chronic catecholamine excess appears to contribute to disease progression and increased mortality in this condition. Therefore, blockade of sympathetic activation represents a logical, if somewhat counter-intuitive, approach to the management of the patient with systolic CHF. Pharmacological approaches to blockade of this system include inhibition of central sympathetic outflow (using central sympatholytics, e.g. rilmenidine, **moxonidine**), blockade of the catecholamine biosynthetic pathway (dopamine beta hydroxylase antagonists) and blockade of the cardiac effects of sympathetic activation (beta-adrenoceptor blocking agents). Beta-blockers have now been extensively studied in patients with symptomatic CHF of the New York Heart Association (NYHA) Class II and III severity. Provided beta-blocker therapy is carefully up-titrated from sub-therapeutic doses and given for at least three to four months, these agents have been associated with favourable long term haemodynamic, functional and mortality outcomes. Furthermore, beta-blockers delay disease progression in CHF by reversing the pathological myocardial remodelling process that accompanies the disease. Non-selective beta-adrenoceptor blocking drugs appear to be of particular benefit in CHF therapy. Myocardial beta2 receptors are down-regulated to a lesser extent than beta1 receptors in CHF, therefore blockade of the beta2 receptor sub-type may assume greater importance in inhibiting the deleterious effects of sympathetic activation on the

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myocardium in this disease. Newer agents that possess additional vasodilator properties (carvedilol, bucindolol, nebivolol) may be useful in overcoming the initial negative inotropy of the beta-blocking component of the drug, however, it is unlikely that vasodilation contributes greatly to long term clinical benefits. Drugs such as carvedilol are also anti-oxidant, anti-proliferative and have anti-endothelin actions; the clinical significance of these properties is yet to be determined. Unanswered questions remain regarding the use of beta-blockers in heart failure. Ongoing studies are further examining mechanisms underlying the clinical benefits of these agents as well as their therapeutic potential in NYHA Class IV patients, **heart failure** post-**myocardial infarction** and patients with asymptomatic left ventricular dysfunction.

L50 ANSWER 9 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:71837 Document No.: PREV199900071837. I1-Imidazoline agonist **moxonidine** decreases sympathetic nerve activity and blood pressure in hypertensives. Wenzel, Rene Roland; Spieker, Lukas; Qui, Su; Shaw, Sidney; Luescher, Thomas Felix; Noll, Georg (1). (1) Dep. Cardiol., Univ. Hosp., CH-8091 Inselspital Bern Switzerland. Hypertension (Dallas), (Dec., 1998) Vol. 32, No. 6, pp. 1022-1027. ISSN: 0194-911X. Language: English.

→ have full article

AB **Moxonidine** is an I1-imidazoline receptor agonist that reduces blood pressure in hypertensives. Experimental data suggest that **moxonidine** inhibits central sympathetic activity. However, whether such a mechanism is involved in vivo in humans is still unclear. We investigated the effects of 0.4 mg **moxonidine** orally on muscle sympathetic nerve activity and heart rate in an open study in 8 healthy volunteers. Furthermore, we studied the effects of 0.4 mg **moxonidine** on muscle sympathetic nerve activity, heart rate, blood pressure, 24-hour blood pressure profile, and hormone plasma levels in 25 untreated hypertensives in a double-blind, placebo-controlled study. **Moxonidine** decreased muscle sympathetic nerve activity in both healthy volunteers ($P<0.05$ versus baseline) and hypertensives ($P<0.02$ versus placebo). Plasma norepinephrine also decreased ($P<0.01$), whereas plasma epinephrine and renin levels did not change (P=NS). Furthermore, **moxonidine** decreased systolic ($P<0.0001$) and diastolic ($P<0.001$) blood pressure. Heart rate decreased after **moxonidine** in healthy subjects ($P<0.05$); in hypertensives, heart rate decreased during the night hours ($P<0.05$) but not during daytime (P=NS). Plasma levels of LDL, HDL, and total cholesterol were not influenced by the drug (P=NS). **Moxonidine** decreases systolic and diastolic blood pressure by inhibiting central nervous sympathetic activity. This makes this new drug suitable for the treatment of human hypertension and possibly for other cardiovascular diseases with increased sympathetic nerve activity, ie, ischemic heart disease and heart failure.

L50 ANSWER 10 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998192362 EMBASE Catecholamine levels and treatment in chronic heart failure. Anker S.D.. Dr. S.D. Anker, Department of Cardiac Medicine, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, United Kingdom. European Heart Journal 19/SUPPL. F (F56-F61) 1998. Refs: 57.
ISSN: 0195-668X. CODEN: EHJODF. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Neurohormonal activation is well studied in chronic heart failure, and covers aspects such as abnormalities of plasma catecholamines, particularly since plasma noradrenaline levels have been found to predict impaired prognosis in heart failure patients. This review will concentrate on the information available on circulating levels of adrenaline and noradrenaline. It will discuss how catecholamine levels change during different disease stages from **myocardial infarction** to severe chronic heart failure. It has been clearly shown that angiotensin

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converting enzyme (ACE) inhibitors exert particularly beneficial effects in heart failure patients with raised catecholamine levels. Nevertheless, reviewing how a variety of drug and non-drug interventions affect catecholamine levels and patients' survival, it is concluded that the effect on catecholamine levels does not directly correlate with a survival benefit of the respective intervention. Despite their prognostic significance, due to the development of new prognostic markers for patients with chronic heart failure, the overall clinical value of spot catecholamine levels remains limited.

L50 ANSWER 11 OF 19 MEDLINE DUPLICATE 5
1998193823 Document Number: 98193823. PubMed ID: 9532644. [Efficacy of **moxonidine**, an imidazoline receptor agonist, in patients with essential hypertension]. Opyt primeneniia agonista imidazolinovykh retseptorov moksonidina u bol'nykh gipertonicheskoi bolezn'iu (sobstvennoe nabliudenie). Baliakina E V; Patrusheva I F; Rynskova E E; Iurenev A P. TERAPEVTICHESKII ARKHIV, (1998) 70 (1) 15-9. Journal code: VLU; 2984818R. ISSN: 0040-3660. Pub. country: RUSSIA: Russian Federation. Language: Russian.
AB AIM: Study of zint (**moxonidine**), a hypotensive drug with the central mechanism of action. MATERIALS AND METHODS: The hemodynamics and platelet functional activity were assessed in 30 patients with essential hypertension treated by zint in a daily dose of 0.4 mg, taken in the morning, for 3 months. RESULTS: By the end of treatment the systolic arterial pressure decreased by 23 +/- 4 mm Hg, diastolic by 15 +/- mm Hg, mean pressure by 17 +/- 2 mm Hg, and heart rate by 5 +/- 4 str/min. Echography showed that **myocardial hypertrophy** decreased but negligibly. An evident decrease of ADP-induced platelet aggregation was observed. CONCLUSION: Zint therapy may be a most physiological method of arterial hypertension control.

L50 ANSWER 12 OF 19 EMBASE 
97346240 EMBASE Document No.: 1997346240. [Microvascular coronary artery disease in hypertension]. MICROVASCULARIS CORONARIABETEGSEG HYPERTONIABAN. Lengyel M.. Dr. M. Lengyel, Pf. 88, H-1450 Budapest, Hungary. Lege Artis Medicine 7/10 (620-625) 1997.
Refs: 47.
ISSN: 0866-4811. CODEN: LAMEFU. Pub. Country: Hungary. Language: Hungarian. Summary Language: Hungarian; English.
AB The cause of myocardial ischaemia without major coronary artery disease is microvascular coronary artery disease. The pathophysiological basis of microvascular ischaemia is impaired coronary flow reserve (CFR). Microvascular ischaemia is most frequently associated to hypertension. It is a syndrome of typical chest pain, positive ECG or thallium stress test and normal coronary angiogram. The diagnostic technique of choice is the measurement of CFR reduction at iv. dipyridamole or adenosine infusion. Two main mechanisms account for abnormalities of the coronary microcirculation: myocardial and vascular. **Myocardial hypertrophy** in combination with increased wall stress may contribute to the reduction of CFR. Interstitial fibrosis including perivascular fibrosis was proposed to be another etiologic factor of impaired coronary microcirculation. Hypertensive remodelling of the coronary microcirculation includes the reduction of vascular density and the increase of the wall/lumen ratio of the small intramyocardial vessels. These alterations can be measured in humans using endomyocardial biopsy. The most important functional factor responsible for microvascular coronary artery disease is endothelial dysfunction, assessed by intracoronary acetilcholin infusion. Microvascular coronary artery disease may be associated with hypertensive heart failure. Hypertensive microvascular coronary artery disease can be reversible, therefore the goals of antihypertensive therapy include not only blood pressure control, regression of hypertrophy and prevention of interstitial fibrosis but also

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the regression of microvascular abnormalities. Such combined effect can be expected from ACE inhibitors, calcium antagonists and **moxonidine**
.

L50 ANSWER 13 OF 19 MEDLINE
97269725 Document Number: 97269725. PubMed ID: 9156911. [Imidazoline receptors and use of drug blocking receptors I1]. Receptory imidazolinowe i stosowanie lekow blokujacych receptory 11. Lada W. (Katedry i Kliniki Kardiologii AM w Warszawie, Szpital Brodnowski. ) POLSKI MERKURIUSZ LEKARSKI, (1996 Aug) 1 (2) 124-5. Ref: 10. Journal code: CTL; 9705469. ISSN: 1426-9686. Pub. country: Poland. Language: Polish.

AB Imidazoline-preferring receptors are important in the pathophysiology of hypertension. The selective 11-receptor agonists are **moxonidine**, cimetidine and rilmenidine. Some clinical studies indicate the usefulness of **moxonidine** therapy in hypertension, arrhythmias and acute **myocardial infarction**.

L50 ANSWER 14 OF 19 MEDLINE DUPLICATE 6
96139233 Document Number: 96139233. PubMed ID: 8582695. [Coronary microangiopathy in hypertensive heart disease: pathogenesis, diagnosis and therapy]. Koronare Mikroangiopathie bei hypertensiver Herzkrankheit: Pathogenese, Diagnostik und Therapie. Motz W; Scheler S; Strauer B E. (Klinik und Poliklinik fur Innere Medizin B, Ernst-Moritz-Arndt-Universitat Greifswald, Zentrum fur Kardiologie. ) HERZ, (1995 Dec) 20 (6) 355-64. Ref: 52. Journal code: F88; 7801231. ISSN: 0340-9937. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

AB Coronary reserve plays an important role in myocardial oxygen supply. During rest, oxygen consumption is near to maximal. An increase in myocardial oxygen demand can only be covered by an increase in coronary flow by dilation of coronary vessels. The maximal achievable rise in coronary blood flow is called coronary reserve. Coronary reserve is not only enhanced in patients with coronary artery disease but also in patients with disorders of coronary microcirculation for example in arterial hypertension. The following review will deal especially with disorders of the microcirculation in arterial hypertension. The impairment of coronary reserve is a result of structural and functional alterations. Structural alterations include an increase in media wall thickness of the small coronary arteries and a reduction of coronary capillaries. Extravascular myocardial forces which determine coronary resistance include **myocardial hypertrophy** and qualitative changes of myocardium like interstitial and perivascular fibrosis. The role of functional alterations like endothelial related vasomotion is discussed. The renin-angiotensin system modulates the growth of the small muscle cells of the vessels and induces protooncogenes and other growth factors. Therefore the renin-angiotensin system may also play an important role in hypertensive remodeling. Hypertensive coronary microangiopathy is diagnosed by exercise stress test and ST-segment-monitoring over 24 hours to show myocardial ischemia. Also nuclear medicine technics can be used if conventional methods of showing ischemia don't work. The diagnosis is definite if the determination of coronary reserve shows that the maximal coronary blood flow is not achieved. Coronary flow can be measured by the argon-gas-method, the thermodulation-technic or by the doppler-method. Also by nuclear medicine technics (PET) the coronary flow reserve can be determined. The advantages of these methods are discussed. In experimental studies calcium-channel-blockers, ACE-inhibitors and **moxonidine** showed an increase in density of capillaries and also a reduction of **myocardial hypertrophy**, which both result in an improvement of coronary reserve. Clinical studies of our group demonstrate that coronary microangiopathy in hypertensives can be improved by calcium-channel-blockers and ACE-inhibitors after one year treatment. Beta-receptor-blockers show no clear improvement of coronary reserve. It

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has to be shown by further studies whether the improvement of coronary reserve is more important for prognosis than the regression of **myocardial hypertrophy**.

L50 ANSWER 15 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
94110556 EMBASE Document No.: 1994110556. [Benefits and risks of antihypertensive therapy from the cardiologic point of view]. NUTZEN UND RISIKEN DER HOCHDRUCKTHERAPIE AUS KARDIALER SICHT. Motz W.; Strauer B.E.. Medizinische Klinik und Poliklinik B, Heinrich-Heine-Universitat, Moorenstr. 5,40225 Dusseldorf, Germany. Zeitschrift fur Kardiologie 83/3 (179-187) 1994.
ISSN: 0300-5860. CODEN: ZKRDAX. Pub. Country: Germany. Language: German. Summary Language: English; German.

AB The poor prognosis of arterial hypertension is mainly determined by its cardiac organ damages. Even borderline arterial hypertension significantly increases coronary morbidity and mortality, particularly in the presence of other risk factors such as hypercholesterolemia, diabetes, and cigarette smoking. Arterial hypertension causes **myocardial hypertrophy** and fibrosis, and affects coronary microcirculation by structural and functional changes of the small intramural resistance arteries, rarefication of arterioles and capillaries and a distinct disturbance of endothelial vasomotion (i.e. 'hypertensive remodeling'). Moreover, the presence of arterial hypertension predisposes to atherosclerotic coronary artery disease. Regarding the benefit-risk-ratio of antihypertensive therapy, benefit is much greater than risk: 1) An antihypertensive treatment with ACE-inhibitors, calcium channel blockers, beta-receptor blockers and anti-sympathicotonic substances leads to both reversal of LV hypertrophy and improvement of coronary flow reserve. 2) Incidence of hypertensive heart failure has dropped considerably during the last 20 years. 3) Intervention studies have shown at least a clear tendency of a reduction in coronary morbidity and mortality. 4) In patients with coronary artery disease diastolic blood pressure should not be lowered under 85 mmHg (J-curve). 5) An antihypertensive treatment should not adversely influence blood lipids when cholesterol is elevated. 6) Even in very elderly patients medical intervention to lower blood pressure is indicated from the cardiologic point of view (SHEP- and SHOP-studies).

L50 ANSWER 16 OF 19 MEDLINE DUPLICATE 7
95182597 Document Number: 95182597. PubMed ID: 7533225. Therapy of hypertensive cardiac hypertrophy and impaired coronary microcirculation. Motz W; Strauer B E. (Medical Clinic B, Heinrich-Heine University of Dusseldorf, Germany. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1994) 24 Suppl 1 S34-8. Ref: 33. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB In arterial hypertension, cardiac remodeling comprises myocyte hypertrophy, interstitial fibrosis, and functional and structural alterations of the coronary microcirculation. This leads to diastolic and systolic dysfunction of the left ventricle and impairment of coronary flow reserve. Consequently, antihypertensive treatment should aim at repairing hypertensive cardiac remodeling through reversing myocyte **hypertrophy**, restoring **myocardial** structure, and improving coronary flow reserve along with blood pressure normalization. Although it has been shown that regression of left ventricular hypertrophy (LVH) can be achieved by suitable antihypertensive therapy, more insight regarding the ability to repair coronary microcirculation is needed. In spontaneously hypertensive rats (SHRs), it has been shown that coronary reserve was enhanced after hydralazine administration without concomitant regression of LVH. Likewise, administration of the calcium-channel blocker felodipine led to a reversal of medial hypertrophy in coronary resistance vessels. The angiotensin-converting enzyme inhibitor lisinopril was shown to improve coronary reserve and to reserve both medial **hypertrophy**

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and **myocardial** fibrosis in SHRs. Increase in length density of capillaries with either nifedipine or **moxonidine** treatment was also found in experimental hypertension. First clinical data indicate that, after prolonged antihypertensive treatment, coronary flow reserve can be improved in hypertensive patients with microvascular disease. Further studies are warranted to elucidate whether improved coronary flow reserve after medical treatment for arterial hypertension is due to an influence of myocardial factors, such as LVH or myocardial fibrosis or to repair of the structurally remodeled microcirculation.

L50 ANSWER 17 OF 19 MEDLINE DUPLICATE 8
95182599 Document Number: 95182599. PubMed ID: 7533227. Effect of **moxonidine** on arrhythmias induced by coronary artery occlusion and reperfusion. Lepran I; Papp J G. (Department of Pharmacology, Albert Szent-Gyorgyi Medical University, Szeged, Hungary. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1994) 24 Suppl 1 S9-15. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.
AB The aim of the present study was to investigate the influence of **moxonidine**, a representative of I1-imidazoline-receptor agonist, on arrhythmias induced by myocardial ischemia or reperfusion. Acute **myocardial infarction** was produced by tightening a previously placed loose silk loop around the coronary artery in conscious rats. **Moxonidine** (0.01, 0.03, or 0.10 mg/kg i.v., 10 min before coronary ligation) significantly decreased the incidence of ventricular tachycardia during the first 15 min of infarction (70 versus 100% in controls), and the number of animals that survived without developing any arrhythmia was increased (15, 20, and 25%, respectively, versus 0%). Reperfusion-induced arrhythmias were produced by releasing a snare after 6 min of myocardial ischemia in anesthetized, artificially ventilated rats. Reperfusion rapidly induced severe dysrhythmias in all of the control animals. **Moxonidine** pretreatment (0.03 and 0.10 mg/kg) decreased the incidence of ventricular fibrillation (25 and 30% versus 64%) and increased the number of animals that survived without developing any arrhythmia (20 and 25% versus 0%). We conclude that **moxonidine** offers significant protection against the development of arrhythmias induced by acute regional myocardial ischemia in conscious rats. **Moxonidine** pretreatment also provides a beneficial effect during reperfusion-induced arrhythmias that appear after a brief period of myocardial ischemia.

L50 ANSWER 18 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
93137542 EMBASE Document No.: 1993137542. Coronary microcirculating in hypertensive heart disease: Functional significance and therapeutic implications. Motz W.; Vogt M.; Strauer B.E.. Medizinische Einrichtung, Heinrich-Heine-Universitat, Medizinische Klinik/Poliklinik B, Moorenstrasse 5,W-4000 Dusseldorf 1, Germany. Clinical Investigator, Supplement 71/5 (S42-S45) 1993.
ISSN: 0941-2719. CODEN: CISUEU. Pub. Country: Germany. Language: English. Summary Language: English.
AB In arterial hypertension left ventricular hypertrophy comprises myocyte hypertrophy, interstitial fibrosis and structural alterations of the coronary microcirculation. This leads to an impairment of diastolic function of the left ventricle and coronary flow reserve despite normal epicardial arteries. Consequently, antihypertensive treatment should aim at reversing myocyte **hypertrophy**, restoring **myocardial** structure and improving coronary flow reserve along with blood pressure normalization.

L50 ANSWER 19 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
92300979 EMBASE Document No.: 1992300979. Pharmacotherapeutic effects of antihypertensive agents on myocardium and coronary arteries in hypertension. Motz W.; Vogt M.; Scheler S.; Strauer B.E.. Med

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Einrichtungen der H.-Heine-Univ, Mediznische Klinik und Poliklink B, Abt Kardiol, Pneumol und Angiologie, Moorenstrasse 5,D-4000 Dusseldorf 1, Germany. European Heart Journal 13/SUPPL. D (100-106) 1992.
ISSN: 0195-668X. CODEN: EHJODF. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Hypertensive left ventricular hypertrophy comprises myocyte hypertrophy interstitial fibrosis and structural alterations in the coronary microcirculation. This leads to impairment of diastolic function in the left ventricle and coronary flow reserve despite normal epicardial arteries. Consequently, antihypertensive treatment should aim at (1) reversing myocyte **hypertrophy**, (2) restoring **myocardial** structure and (3) improving coronary flow reserve without lowering blood pressure. In recent years many clinical studies have shown that regression of hypertensive hypertrophy can be induced by long-term treatment with ACE inhibitors, calcium-channel blockers, beta-receptor blockers and antisympathonic drugs. However vasodilators and diuretics which stimulate adrenoceptor activity and increase angiotensin II levels were found to be less effective in reversing left ventricular hypertrophy. The trophic influence of catecholamines and angiotensin II on the myocardium counteracts the effect of systolic wall stress reduction due to blood pressure lowering. As regards reversal of interstitial fibrosis, ACE inhibitors seem to be effective because fibroblast growth was found to be stimulated by angiotensin II. Recently, clinical studies have confirmed previous experimental data that improvement in impaired coronary vasodilator reserve can be realized by long-term antihypertensive therapy. In adopting an antihypertensive treatment strategy prime consideration should be given to reversal of cardiac remodelling through restoration of myocardial structure and repair of the coronary microcirculation.

MISSING TERM 'REPERFUS> OR'.
The search profile that was entered contains a logical operator followed immediately by another operator.

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=> s (135 or 142) and (post myocardia? or ischemic myocardi? or heart muscle
necrosis or thrombolytic or fibrinolytic therap? or reperfus? or sympathetic
nervous system or heart fail? or cardi? hypertroph?)
L51          76 FILE MEDLINE
L52          47 FILE CAPLUS
L53          56 FILE BIOSIS
L54         121 FILE EMBASE
L55           4 FILE WPIDS
L56           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L57         304 (L35 OR L42) AND (POST MYOCARDIA? OR ISCHEMIC MYOCARDI? OR HEART
                 MUSCLE NECROSIS OR THROMBOLYTIC OR FIBRINOLYTIC THERAP? OR
                REPERFUS? OR SYMPATHETIC NERVOUS SYSTEM OR HEART FAIL? OR CARDI?
                 HYPERTROPH?)

=> s l57 not l49
L58          72 FILE MEDLINE
L59          43 FILE CAPLUS
L60          50 FILE BIOSIS
L61         112 FILE EMBASE
L62           3 FILE WPIDS
L63           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L64         280 L57 NOT L49
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=> dup rem l64
PROCESSING COMPLETED FOR L64
L65          184 DUP REM L64 (96 DUPLICATES REMOVED)

=> s l64 and (therap? or treat?)
L66           50 FILE MEDLINE
L67           28 FILE CAPLUS
L68           22 FILE BIOSIS
L69          101 FILE EMBASE
L70            3 FILE WPIDS
L71            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L72          204 L64 AND (THERAP? OR TREAT?)

=> dup rem l72
PROCESSING COMPLETED FOR L72
L73          137 DUP REM L72 (67 DUPLICATES REMOVED)

=> d 1-137 cbib abs hitstr

L73  ANSWER 1 OF 137  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002023979  EMBASE  Does it make sense to develop new centrally acting
     cardiovascular drugs?. Bousquet P.; Monassier L.; Feldman J.. P. Bousquet,
     Lab. Neurobiologie et Pharmacologie, Universite Louis Pasteur, Faculte de
     Medecine, 11 rue Humann, 67000 Strasbourg, France.
     Pascal.Bousquet@medecine.u-strasbg.fr. Clinical and Experimental
     Pharmacology and Physiology  28/12 (976-978)  2001.
     Refs: 27.
     ISSN: 0305-1870. CODEN: CEXPB. Pub. Country: Australia. Language: English.
     Summary Language: English.
AB   1. The autonomic nervous system plays a pivotal role in modulating all the
     components of the cardiovascular regulation. Therefore, one can assume
     that drugs targeting this system may be useful in the management of
     several cardiovascular diseases. 2. Drugs acting on central nervous system
     centres seem to be modulators rather than blockers; as such, they are
     expected to preserve the contraregulatory processes and to generate only a
     few side effects. 3. Because the sympathetic nervous
     system is largely involved in the regulation of vasomotor tone,
     centrally acting anti-hypertensive drugs were developed first. 4.
     Recently, new leader compounds selective for non-adrenergic imidazoline
     recepetors have been synthetized. Although such drugs have no capacity to
     activate .alpha.(2)-adrenoceptors, they have been proven to be
     hypotensive. These drugs are expected to be even better tolerated than the
     currently available centrally active drugs. They may also have additional
     beneficial effects. 5. Here, the experimental evidence suggesting that
     such drugs may be useful in the management of some cardiac arrhythmias
     and/or left ventricular dysfunction will be reviewed.

L73  ANSWER 2 OF 137     MEDLINE
2001637420  Document Number: 21546176.    PubMed ID: 11693029.    [ACE-dependent
     and sympathetic components of blood pressure regulation in patients with
     essential hypertension].    APF-zavisimyi i simpaticheskii komponenty
     reguliatsii arterial'nogo davleniia u patsientov s essentsial'noi
     gipertoniei. Aparina T V; Gomazkov O A; Dilakian E A; Britov A N.
     (National Research Centre for Preventive Medicine, Pogodinskaja St., 10,
     Moscow, Russia, 119992 Moscow. ) VOPROSY MEDITSINSKOI KHIMII, (2001
     Jul-Aug) 47 (4) 411-8.  Journal code: 0416601. ISSN: 0042-8809. Pub.
     country: Russia: Russian Federation. Language: Russian.
AB   The development of arterial hypertension is accompanied by impairment of
     the normal ratio of the "ACE-depending" and of the sympathetic
     nervous system, correlates with the action on the main

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pharmacological "targets": I-I-imidazoline receptors (**moxonidine** ) or the ACE activity (enalapril). The aim of the present investigation was to determine the hypotensive and metabolic effects of **moxonidine** and enalapril depending on the basal ACE activity in patients with arterial hypertension, complicated with the metabolic syndrome. Effectiveness of **moxonidine** and enalapril administration (during 24 weeks) depended on the basal ACE activity in the hypertensive patients: (a) in the group of patients with low basal ACE activity **moxonidine** very effectively decreased systolic and diastolic blood pressure, compared with the group of patients with high basal ACE activity; (b) influence of enalapril on the level of arterial blood pressure was more pronounced with high basal ACE activity. In conclusion: choosing a hypotensive **treatment** for patients with the metabolic syndrome, it is advisable to take into account the basal ACE activity levels.

L73 ANSWER 3 OF 137 MEDLINE
2001552444 Document Number: 21486092. PubMed ID: 11600937. Central imidazoline (I(1)) receptors modulate aqueous hydrodynamics. Ogidigben M J; Potter D E. (Department of Pharmacology, Merck & Co, Inc., Merck Research Laboratories, West Point, Pennsylvania, USA. ) CURRENT EYE RESEARCH, (2001 May) 22 (5) 358-66. Journal code: DUB; 8104312. ISSN: 0271-3683. Pub. country: England: United Kingdom. Language: English.

AB The purpose of this work is to determine the relative contributions of central imidazoline (I(1)) receptors to the ocular hydrodynamic action of **moxonidine**. **Moxonidine** (MOX), an alpha(2) and I(1) receptor agonist, and efaroxan (EFA), a relatively selective I(1) antagonist, were utilized to study alterations in intraocular pressure (IOP) and aqueous flow in New Zealand white rabbits subjected to intracerebroventricular (i.c.v.) cannulation and sympathectomy. Intracerebroventricular administration of MOX (0.033, 0.33 and 3.33 microg) to normal rabbits produced dose-dependent, bilateral IOP decreases of 3, 6, and 8 mmHg, respectively. The ocular hypotensive response to MOX was immediate (10 min. post drug), lasted for one hour, and was inhibited by prior administration of efaroxan (3.33 microg i.c.v.). In unilaterally sympathectomized (SX) rabbits, the ocular hypotensive response induced by i.c.v MOX in the denervated eye was attenuated approximately 50%, but the duration of ocular hypotension in the surgically altered eye was longer than that of the normal eye. MOX (0.33 microg i.c.v.), caused a statistically significant decrease (2.24 to 1.59 ml/min.) in aqueous flow in normal eyes. In SX eyes, there was no change in aqueous flow by MOX, suggesting that IOP effect in i.c.v. MOX observed in the SX eye might be mediated by changes in outflow resistance. Sedation was observed in all the rabbits **treated** with MOX (i.c.v.) and was dose-dependent. These in vivo data support the suggestion that centrally located I(1) receptors modulate the early contralateral response to topically administered MOX and are involved in lowering of IOP and aqueous flow in rabbit. In addition, expression of the full ocular hypotensive effect of centrally applied MOX depends on intact sympathetic innervation. Ocular hypotension induced by MOX in the SX eye may involve an effect on uveoscleral outflow.

L73 ANSWER 4 OF 137 MEDLINE DUPLICATE 1
2002009492 Document Number: 21235135. PubMed ID: 11336590. **Moxonidine**: some controversy. Doggrell S A. (Doggrell Biomedical Communications, 47 Caronia Crescent, Lynfield, Auckland, New Zealand. ) Expert Opin Pharmacother, (2001 Feb) 2 (2) 337-50. Journal code: 100897346. ISSN: 1465-6566. Pub. country: England: United Kingdom. Language: English.

AB Initially it was considered that **moxonidine**, like clonidine, acted at central (2)-adrenoceptors to reduce blood pressure. With the characterisation of imidazoline binding sites distinct from

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(2)-adrenoceptors, the consensus became that **moxonidine** was acting predominantly at imidazoline I(1) receptors in the rostral ventrolateral medulla to lower blood pressure. **Moxonidine** acts at prejunctional (2)-adrenoceptors on sympathetic nerve endings to decrease noradrenaline release and this may contribute to its ability to lower blood pressure. The predominant site of action of **moxonidine** may also depend on route of administration, with imidazoline I(1) receptors being predominant after central, and (2)-adrenoceptors predominant after systemic administration. The controversy over the mechanism and site of action with **moxonidine** is ongoing. In animal models, **moxonidine** lowers blood pressure, reduces **cardiac hypertrophy** and remodelling, reduces cardiac arrhythmias and increases blood flow in cerebral ischaemia. **Moxonidine** also has beneficial effects in animal models of diabetes and kidney disease. **Moxonidine** increases sodium and water excretion in rats, but not humans. Animal studies indicate that **moxonidine** may be useful in the **treatment** of glaucoma by reducing intra-ocular pressure. Animal studies show that **moxonidine** may also be effective in pain and in ethanol withdrawal. In humans, the pharmacokinetics of **moxonidine** are of the one-compartment model with first-order absorption. Renal elimination is the major route of elimination and individual titration of **moxonidine** is needed in patients with renal impairment. There is overwhelming evidence that **moxonidine** is a safe and effective antihypertensive. A large clinical trial of **moxonidine** in **heart failure**, MOXCON, was stopped because of excessive deaths in the **moxonidine** group. **Moxonidine** should not be used in patients with **heart failure**, but there are no obvious reasons to stop its use as an antihypertensive, or its development for other clinical uses.

L73 ANSWER 5 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002007663 EMBASE Sixteenth annual meeting of the American Society for Hypertension San Francisco, CA, USA May 15-19, 2001. Scriabine A.. Dr. A. Scriabine, Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06420, United States. alexander.scriabine@snet.net. Cardiovascular Drug Reviews 19/3 (263-277) 2001.
ISSN: 0897-5957. CODEN: CDREEA. Pub. Country: United States. Language: English.

L73 ANSWER 6 OF 137 MEDLINE DUPLICATE 2
2001350830 Document Number: 21307495. PubMed ID: 11413801. [**Treatment** of hypertension in obesity]. Behandlung der Hypertonie bei Adipositas. Scholze J; Sharma A M. (Medizinische Poliklinik, Campus Mitte, Charite, Berlin.. juergen.scholze@charite.de) . HERZ, (2001 May) 26 (3) 209-21. Ref: 109. Journal code: F88; 7801231. ISSN: 0340-9937. Pub. country: Germany: Germany, Federal Republic of. Language: German.
AB BACKGROUND: Hypertension and obesity are common medical conditions independently associated with increased cardiovascular risk. Many large epidemiological studies have demonstrated associations between body mass index and blood pressure, and there is evidence to suggest, that obesity is a causal factor in the development of hypertension in obese subjects. Weight Reduction and maintenance is an essential first step in the **treatment** of obesity-associated hypertension. Weight reduction may be achieved by behavior modification, diet, and exercise or by the use of anti-obesity medication. However, the long-term outcomes of weight management programs for obesity are generally poor, and most hypertensive patients will require antihypertensive drug **therapy**.
PATHOPHYSIOLOGY: Obese hypertensive patients often have metabolic abnormalities known to be exacerbated by commonly used antihypertensive agents but also obesity per se is often associated with endorgan damage

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including left ventricular hypertrophy, glomerular hyperfiltration and microalbuminuria, congestive **heart failure** or sudden cardiac death. Furthermore they have revealed volume expansion, increased cardiac output, and lower total peripheral resistance than lean patients. Hypertension in obese patients appears to be related to both increased **sympathetic nervous system** activity and activation of the renin-angiotensin system. Where antihypertensive **therapy** is necessary, the aim should be to use agents based on the hemodynamic and metabolic background and that have benefits beyond blood pressure lowering and improve the conditions most commonly linked with obesity-associated hypertension, such as hyperlipidaemia, Type II diabetes, left ventricular hypertrophy, coronary artery disease, or congestive **heart failure**. PHARMACOTHERAPY: Based on their favorable metabolic profiles, it would appear that ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, **moxonidine** and alpha-blockers can lower blood pressure without worsening the metabolic abnormalities, that is just one aspect of the problem. Yet, most guidelines fail to provide specific advice on the pharmacological management of hypertension in obese patients. This may be due to the fact that there are currently no studies that have addressed the efficacy of specific antihypertensive agents in reducing mortality in obese-hypertensive patients. This paper reviews the theoretical reasons for the differential use of the major classes of antihypertensive agents in the pharmacological management of obesity-related hypertension and also considers the potential role of anti-obesity agents.

L73 ANSWER 7 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001389221 EMBASE Antihypertensive **treatment** and cardiovascular risk management in patients with the metabolic syndrome - Focus on SNS and insulin resistance. Keulen L.; Lang R.; Henriksen E.J.; Jacob St.. Dr. St. Jacob, Albert Schweitzer Klinik, Parkstrasse 10, D-78126 Konigsfeld, Germany. Jacob@ask.mediclin.de. Journal of Clinical and Basic Cardiology 4/3 (193-195) 2001.
Refs: 30.
ISSN: 1561-2775. CODEN: JCBCFT. Pub. Country: Austria. Language: English. Summary Language: English.

AB Essential hypertension is very frequently associated with an over-activity of the **sympathetic nervous system** (SNS) and a decrease in insulin sensitivity of skeletal muscle glucose uptake, even when glycaemic control is (still) normal. In hypertensive patients, two major functions of insulin are impaired: there is insulin resistance of peripheral glucose uptake (primarily skeletal muscle) and insulin resistance of insulin-stimulated vasodilation. This insulin resistance is very often associated with dyslipidaemia, obesity, hypertension and impaired glucose tolerance, a cluster termed the "metabolic syndrome or the insulin resistance syndrome". Meta-analyses of antihypertensive intervention studies indicate a less than expected reduction of coronary events ("the coronary paradox"), although blood pressure had been lowered. These findings suggest, that lowering blood pressure is not enough. Furthermore, retrospective and very recent prospective data showed a higher incidence of type 2 diabetes in subjects **treated** with beta-blocking agents. Thus, the metabolic side effects of the antihypertensive **treatment** need to receive more attention. In the metabolic syndrome, a reduction of SNS drive would seem to be specifically effective. However, many groups have shown that antihypertensive **treatment** with beta-blockers, decreases insulin sensitivity by various mechanisms. In contrast the centrally acting agent **moxonidine**, an imidazoline I1- receptor agonist, may be of interest in this context. It inhibits sympathetic outflow and causes vasodilation. **Moxonidine treatment** improved insulin sensitivity specifically in insulin-resistant, obese patients with mild hypertension. Animal studies indicate an improvement of insulin-stimulated

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glucose uptake into the skeletal muscle and an improvement of glucose tolerance. Therefore, the beneficial characteristics of these newer class of antihypertensive agents suggest, that **moxonidine** could be advantageous for hypertensive patients with insulin resistance or type 2 diabetes. However, long-term studies are needed to confirm these benefits. In the cardiovascular risk management, lowering blood pressure is just one cornerstone. Due to the known metabolic "side effects" the selection of the antihypertensive agent might be relevant for the long-term outcome.

L73 ANSWER 8 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001389220 EMBASE Interaction of the **sympathetic nervous system** with other pressor systems in antihypertensive **therapy**. Wenzel R.R.; Bruck H.; Mitchell A.; Schaefers R.F.; Baumgart D.; Erbel R.; Heemann U.; Philipp Th.. Dr. R.R. Wenzel, Department of Nephrology, University Hospital Essen, Hufelandstr. 55, D-45122 Essen, Germany. rene@rrwenzel.de. Journal of Clinical and Basic Cardiology 4/3 (185-192) 2001.
Refs: 139.
ISSN: 1561-2775. CODEN: JCBCFT. Pub. Country: Austria. Language: English. Summary Language: English.

AB Regulation of blood pressure homeostasis and cardiac function is importantly regulated by the **sympathetic nervous system** (SNS) and other pressor systems including the renin-angiotensin system (RAS) and the vascular endothelium. Increases in SNS activity increase mortality in patients with hypertension, coronary artery disease and congestive **heart failure**. This review summarizes some of the interactions between the main pressor systems, ie, the SNS, the RAS and the vascular endothelium including the endothelin-system. Different classes of cardiovascular drugs interfere differently with the SNS and the other pressor systems. Beta-blockers, ACE-inhibitors and diuretics have no major effect on central SNS activity. Pure vasodilators including nitrates, alpha-blockers and DHP-calcium channel blockers increase SNS activity. In contrast, central sympatholytic drugs including **moxonidine** reduce SNS activity. The effects of angiotensin-II receptor antagonist on SNS activity in humans are not clear, experimental data are discussed in this review. There are important interactions between the pressor systems under experimental conditions. Endothelin-A-receptor-antagonists inhibit angiotensin II and noradrenaline induced vasoconstriction. On the other hand, with L-NMMA and yohimbine, .alpha.2-adrenoceptor-mediated endothelial vasodilation can be unmasked. Ongoing and future studies have to assess the impact of combination **therapy** with different antihypertensive classes on SNS activity and on the other pressor systems and establish the ideal combination regarding hard end points, efficacy and side effects. It can be assumed, that in cardiovascular diseases with already enhanced SNS activity drugs, which do not increase SNS activity or even lower it, are preferable. Whether this reflects in lower mortality has to be investigated in intervention trials.

L73 ANSWER 9 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001389219 EMBASE The potential role of sympathetic nerve activity in the development of diabetic nephropathy. Strojek K.. Dr. K. Strojek, Department of Internal Diseases, 3-Maja 13/15, 41-800 Zabrze, Poland. kstrojek@slam.katowice.pl. Journal of Clinical and Basic Cardiology 4/3 (183-184) 2001.
Refs: 23.
ISSN: 1561-2775. CODEN: JCBCFT. Pub. Country: Austria. Language: English. Summary Language: English.

AB Diabetic nephropathy is one of the direst complications of diabetes. Progress in medical science has led to introduction of adequate **therapeutic** methods that can significantly reduce the incidence of this complication, but cannot entirely prevent it. In the recent period

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much attention was dedicated to the role of excessive activation of the **sympathetic nervous system** (SNS) in pathogenesis of kidney diseases. The results of experimental and clinical studies reveal that renal affect is associated with increased activity of the SNS, which may lead to progressive multiorgan injury. However, application of drugs inhibiting the activity of the SNS results in lowering of the rate of development of systemic lesions and progression of the glomerulopathy. Preliminary clinical data show that application of **moxonidine**, SNS inhibitor, in non-hypotensive doses in normotensive patients with type 1 diabetes and microalbuminuria results in decrease of urinary albumin excretion. Non-hypotensive effect of **moxonidine**, leading to decrease in the progression of diabetic nephropathy, should be confirmed in large clinical trials. Administration of SNS-inhibiting drugs may then become a new **therapeutic** option in prevention of microangiopathic diabetic complications.

L73 ANSWER 10 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001085411 EMBASE Antihypertensive drugs and **sympathetic nervous system**. Rabbia F.; Martini G.; Genova G.C.; Milan A.; Chiandussi L.; Veglio F.. Dr. F. Rabbia, Centro Ipertensione, Ospedale S. Vito, Strada S. Vito 34, 10133 Torino, Italy. Clinical and Experimental Hypertension 23/1-2 (101-111) 2001.
Refs: 63.
ISSN: 1064-1963. CODEN: CEHYER. Pub. Country: United States. Language: English. Summary Language: English.

AB Several studies have demonstrated that essential hypertension is accompanied by sympathetic activation, which contributes to blood pressure elevation. Sympathetic activation also has adverse consequences in hypertensive patients beyond initiating blood pressure elevation. There is evidence that neural vaso-constriction has metabolic effects in skeletal muscle, impairing glucose delivery to muscles. In the liver, retarding of post prandial clearance of lipids contributes to hyperlipidemia. Cardiac sympathetic activation is a probable cause of sudden death in hearth failure. A trophic effect of sympathetic activation on cardiovascular growth is also likely, contributing to the development of left ventricular hypertrophy. Consequently, one of the major aims of antihypertensive **therapy** should be to attenuate sympathetic tone. It is possible that, among the antihypertensive drugs available, those inhibiting the **sympathetic nervous system** might best reduce cardiovascular risk.

L73 ANSWER 11 OF 137 MEDLINE DUPLICATE 3
2001167187 Document Number: 21094846. PubMed ID: 11167663.
**Moxonidine** in patients with congestive **heart failure**. Brynne L; McNay J L; Schaefer H G; Swedberg K; Wiltse C G; Karlsson M O. (Department of Pharmacy, Division of Biopharmaceutics and Pharmacokinetics, Uppsala University, Uppsala, Sweden. ) BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (2001 Jan) 51 (1) 35-43. Journal code: AU9; 7503323. ISSN: 0306-5251. Pub. country: England: United Kingdom. Language: English.

AB AIMS: To assess the pharmacodynamics of **moxonidine** in patients with functional NYHA Class II-III congestive **heart failure** (CHF). METHODS: A parallel population pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed to assess the effect of **moxonidine** (0.1, 0.2, 0.3 mg twice daily) and placebo **treatment** on plasma noradrenaline (NA) levels, standing systolic blood pressure (SBP), and heart rate (HR) over 12 weeks in 97 patients with CHF using a parallel group design with dose escalation. A sequential analysis was also developed, where the relative changes in NA concentration were related to both SBP and HR. RESULTS: In the parallel PD analysis, an effect delay was shown for all three end points (NA, SBP, and

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HR). An inhibitory Emax model was used to characterize the concentration-effect relationships. For SBP and HR, the EC50 value increased over time. For NA, there was a positive baseline drift over the 12 weeks; this was interpreted as disease progression. **Moxonidine** delayed this increase by 9.8 weeks. For SBP, there was a circadian pattern at baseline. In the sequential PD analysis, the relationship between the drug response (NA) and SBP or HR was best described by an inhibitory Emax model. No effect delays between the response and effects were found. CONCLUSIONS: Effects of **moxonidine** on NA, SBP, and HR could be quantified by an effect compartment model in the presence of disease progression and circadian variations. Disease progression, as judged by increasing NA levels with time, was delayed by **moxonidine**. A direct relationship was found between NA and SBP/HR.

L73 ANSWER 12 OF 137 MEDLINE DUPLICATE 4
2001490309 Document Number: 21423850. PubMed ID: 11532543. The underreporting of results and possible mechanisms of 'negative' drug trials in patients with chronic **heart failure**. van Veldhuisen D J; Poole-Wilson P A. (Department of Cardiology/Thoraxcentre, University Hospital Groningen, P.O. Box 30001, 9700 RB, Groningen, The Netherlands.. d.j.van.veldhuisen@thorax.azg.nl) . INTERNATIONAL JOURNAL OF CARDIOLOGY, (2001 Aug) 80 (1) 19-27. Ref: 67. Journal code: GQW; 8200291. ISSN: 0167-5273. Pub. country: Ireland. Language: English.

AB Large drug trials have become very important to determine which drugs should be used in the **treatment** of patients with chronic **heart failure** (CHF). When these trials showed "positive" results, publication of the data soon followed, leading to a substantial impact on prescription patterns. In the case of "negative" results, many times they were not published, or were reported as an abstract or as short paper disclosing only the main findings. In this article we will discuss some of these trials that were conducted in the last 10 years, since we believe they may provide insight into the pathophysiology and **treatment** options in CHF.

L73 ANSWER 13 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5
2000:259979 Document No. 132:288794 **Sympathetic nervous system** activity-reducing agents for **treatment** of disease- or age-related weight loss and for enhancement of exercise performance. Anker, Stefan Dietmar; Coats, Andrew Justin Stewart (Imperial College Innovations Limited, UK). PCT Int. Appl. WO 2000021509 A2 20000420, 72 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB3302 19991015. PRIORITY: GB 1998-22458 19981015; GB 1998-22459 19981015; GB 1999-17181 19990723.

AB A method of **treating** wt. loss due to underlying disease in a patient, the method comprising administering to the patient an effective amt. of an agent which reduces **sympathetic nervous system** activity. A method of **treating** wt. loss due to underlying disease in a patient, the method comprising administering to the patient an effective amt. of any one or more of the following: a compd. which inhibits the effect of aldosterone such as an aldosterone antagonist; a chymase inhibitor; a cathepsin B inhibitor; a .beta. receptor blocker; an imidazoline receptor antagonist; a centrally acting .alpha. receptor antagonist; a peripherally acting .alpha. receptor antagonist; a ganglion blocking agent; a drug that has an effect on cardiovascular reflexes and thereby reduces SNS activity such as an opiate; scopolamine; an endothelin receptor antagonist; and a xanthine oxidase inhibitor. The methods are particularly useful in **treating** cardiac cachexia. The **sympathetic nervous system** activity-reducing agents may also be used to **treat** wt. loss due to aging and to enhance exercise performance.

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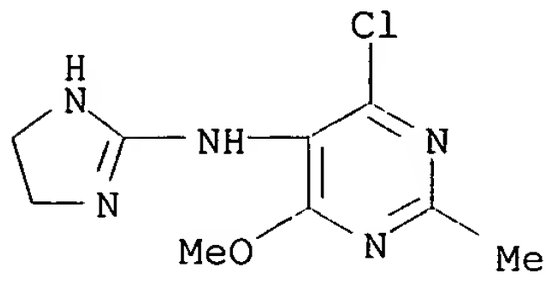
IT **75438-57-2, Moxonidine**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sympathetic nervous system**
activity-reducing agents for **treatment** of disease- or age-related wt. loss and for enhancement of exercise performance)
RN 75438-57-2 CAPLUS
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)




L73 ANSWER 14 OF 137 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-375601 [32] WPIDS
AB US 6066740 A UPAB: 20000706
NOVELTY - Preparation of guanine derivatives (I) or a salt, biohydrolysable ester or protected derivative, comprises forming an isothiourea derivative (II) from an isourea derivative (III) and coupling with an amine (IV).
DETAILED DESCRIPTION - Preparation of guanine derivatives of formula (I) or a salt, biohydrolysable ester or protected derivative, comprises forming an isothiourea derivative of formula (II) from an isourea derivative of formula (III) and coupling with an amine of formula (IV).
R1, R2 = CH3 or C2H5; or
R1+R2 = -(CH2)2- or -(CH2)3- such that they form a 5-6-membered ring;
Z' = alkyl or optionally unsaturated or aromatic mono- or polycyclic carbocycle or heterocycle (containing O, N or S);
R4 = H, alkoxy, alkylthio, alkyl, alkenyl, NH2, COOH, CN, halo, OH, NO2 or SH;
R = CH3, C2H5 or benzyl;
R3 = OR5 or R6;
R5 = allyl, CH3, C2H5, benzyl, tert.-butyl or phenyl; and
R6 = CH3, C2H5, tert.-butyl or phenyl.
USE - The method is useful for making guanine derivatives (e.g. alinidine, iopidine, brimonidine, clonidine, indanazoline, **moxonidine**, tiamenidine, tizanidine, tolonidine and tramazoline) which are useful in the **treatment** of medical disorders, e.g. respiratory, ocular and gastrointestinal disorders, nasal decongestion, hypertension, migraine, disorders associated with **sympathetic nervous system** activity and substance abuse.
ADVANTAGE - The method avoids the need for lengthy, costly or multiple low yielding steps and highly toxic reactants and allows improved yields and product purity and provides additional synthetic flexibility.
Dwg.0/0

L73 ANSWER 15 OF 137 MEDLINE DUPLICATE 6
2000424882 Document Number: 20365971. PubMed ID: 10906160. Effects of low dose sympathetic inhibition on glomerulosclerosis and albuminuria in subtotally nephrectomized rats. Amann K; Rump L C; Simonaviciene A; Oberhauser V; Wessels S; Orth S R; Gross M L; Koch A; Bielenberg G W; Van Kats J P; Ehmke H; Mall G; Ritz E. (Department of Pathology, University of Heidelberg, Germany.. kerstin.amann@patho.imed.uni-erlangen.de) . JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (2000 Aug) 11 (8) 1469-78. Journal

Searched by: Mary Hale 308-4258 CM-1 12D16

code: A6H; 9013836. ISSN: 1046-6673. Pub. country: United States.
Language: English.

AB ABSTRACT.: A potential role of the **sympathetic nervous system** in progression of renal failure has received little attention. This study examined whether nonhypotensive doses of **moxonidine**, an agent that reduces sympathetic activity, affects glomerulosclerosis, urine albumin excretion, and indices of renal handling of norepinephrine (NE) in subtotally nephrectomized (SNX) rats. Sprague Dawley rats were SNX or sham-operated (control). SNX rats were either left untreated or **treated** with **moxonidine** in a dose (1.5 mg/kg body wt per d) that did not modify telemetrically monitored 24-h BP. Glomerular and renal morphology were evaluated by quantitative histology, immunohistochemistry, and in situ hybridization. Urine albumin excretion rate was analyzed by enzyme-linked immunosorbent assay, and kidney angiotensin II and NE content were measured using HPLC, (3)H-NE uptake, and release. Body and kidney weight and BP were not significantly different between SNX with or without **moxonidine**. The glomerulosclerosis index was significantly lower in **moxonidine-treated** (0.88 +/- 0.09) compared with untreated (1.55 +/- 0.28) SNX rats, as was the index of vascular damage (0.32 +/- 0.14 versus 0.67 +/- 0.16). The number of proliferating cell nuclear antigen-positive glomerular and tubular cells per area was significantly higher in untreated SNX rats than in controls and **moxonidine-treated** SNX rats. The same was true for urine albumin excretion rate. Renal angiotensin II tissue concentration was not affected by **moxonidine**. In untreated SNX rats, renal nerve stimulation and exogenous NE induced an increase in isolated kidney perfusion pressure (102 +/- 21 versus 63 +/- 8 mmHg). Renal endogenous NE content was significantly lower in SNX rats than in controls (86 +/- 14 versus 140 +/- 17 pg/mg wet weight). Cortical uptake of [(3)H]-NE was not different, but cortical NE release was significantly higher in SNX rats than in controls. Reduced function of presynaptic inhibitory alpha-adreno-receptors is unlikely because an alpha(2)-adrenoceptor antagonist increased NE release. At subantihypertensive doses, **moxonidine** ameliorates renal structural and functional damage in SNX animals, possibly through central inhibition of efferent sympathetic nerve traffic. In kidneys of SNX rats, indirect evidence was found for increased activity of a reduced number of nerve fibers.

L73 ANSWER 16 OF 137 MEDLINE

2000315986 Document Number: 20315986. PubMed ID: 10856275. Chronic I(1)-imidazoline agonism : sympathetic mechanisms in hypertension.
Greenwood J P; Scott E M; Stoker J B; Mary D A. (Department of Cardiology, St James's University Hospital, Leeds, West Yorkshire, UK.. john_greenwood@hotmail.com) . HYPERTENSION, (2000 Jun) 35 (6) 1264-9.
Journal code: GK7; 7906255. ISSN: 0194-911X. Pub. country: United States.
Language: English.

AB Evidence exists for a state of sympathetic hyperactivity in essential hypertension, and **moxonidine**, a new central sympathetic inhibitor, has been introduced for its **treatment**. Acute administration of **moxonidine** lowers peripheral sympathetic neural output. This study examined the effect of chronic **moxonidine therapy**, at increasing **therapeutic** doses, on resting peripheral sympathetic activity and vascular resistance and their responses to physiological reflex maneuvers. Twelve newly diagnosed patients with essential hypertension were studied sequentially at least 1 month apart, initially on no **therapy**, then on 200 microg, and finally on 400 microg of oral **moxonidine** daily. Changes in heart rate, arterial blood pressure, calf vascular resistance, and peripheral sympathetic drive were assessed at rest and during reflex maneuvers. Peroneal microneurography was used to quantify peripheral sympathetic vasoconstrictor activity by single-unit and multiunit

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techniques. **Moxonidine therapy** progressively reduced resting mean arterial pressure (P<0.0001) without affecting heart rate. At 200 microg daily, there was a significant reduction in sympathetic nerve activity (P<0.001) and calf vascular resistance (P<0.01). At 400 microg daily, further reductions were smaller and insignificant. Responses to cold stimulus and isometric handgrip exercise showed a similar pattern, with the greatest magnitude of change at 200 microg daily. In patients with essential hypertension, chronic **moxonidine therapy** inhibited resting sympathetic vasoconstrictor drive and also its reflex responses. The magnitude of inhibition became less as the **therapeutic** dose was increased, suggesting that **moxonidine** may be more effective under conditions of high sympathetic activity.

L73 ANSWER 17 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000112257 EMBASE Is the lower mortality in patients **treated** with aspirin and angiotensin-converting enzyme inhibitors due to decreased norepinephrine release? (multiple letter) [3]. Levi R.; Maruyama R.; Smith N.C.E.; Seyedi N.; Leor J.; Shmuel G.; Behar S.. Dr. R. Levi, Department of Pharmacology, Cornell Univ. Weill Med. College, 1300 York Avenue, New York, NY, United States. Journal of the American College of Cardiology 35/3 (817-818) 1 Mar 2000.
ISSN: 0735-1097. CODEN: JACCDI.
Publisher Ident.: S 0735-1097(99)00618-X. Pub. Country: United States.
Language: English.

L73 ANSWER 18 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000318954 EMBASE Recent advances in the management of chronic **heart failure**. Krum H.. Prof. H. Krum, Dept. of Epidemiol./Preventive Med., Monash University, Prahran, Vic. 3181, Australia. henry.krum@med.monash.edu.au. Australian and New Zealand Journal of Medicine 30/4 (475-482) 2000.
Refs: 61.
ISSN: 0004-8291. CODEN: ANZJB8. Pub. Country: Australia. Language: English.

L73 ANSWER 19 OF 137 MEDLINE DUPLICATE 7
2000139857 Document Number: 20139857. PubMed ID: 10676687. The effects of **moxonidine**, a novel imidazoline, on plasma norepinephrine in patients with congestive **heart failure**.
**Moxonidine** Investigators. Swedberg K; Bergh C H; Dickstein K; McNay J; Steinberg M. (Department of Medicine, Sahlgrenska University Hospital/Ostra Goteborg, Sweden.. Karl.Swedberg@hjl.gu.se) . JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, (2000 Feb) 35 (2) 398-404. Journal code: H50; 8301365. ISSN: 0735-1097. Pub. country: United States.
Language: English.

AB OBJECTIVE: To evaluate the dose response relationship of **moxonidine** on plasma concentration of norepinephrine during acute and chronic administration in patients with congestive **heart failure** (CHF). BACKGROUND: Sympathetic activation is increased in **heart failure**. **Moxonidine** is an imidazoline ligand acting on the central nervous system (CNS) receptors to decrease sympathetic activation. METHODS: Ninety-seven patients with **heart failure** and New York Heart Association class II-III symptoms and ejection fraction <40% were randomized to placebo or one of three target doses of **moxonidine**, 0.1, 0.2 or 0.3 mg administered twice daily. An initial dose of **moxonidine** 0.1 mg twice a day (b.i.d.) was followed by weekly increments of 0.1 mg b.i.d. until target dose. The second and third study days occurred after four weeks (at target dose) and after 12 weeks, respectively. At each study day, repeated blood samples were drawn. RESULTS: There was a significant dose-related decrease of systolic blood pressure across all three study days. Heart rate decreased significantly on study day 3 in a dose-related manner. The acute 2 h

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decrease in plasma norepinephrine in response to all three doses of **moxonidine** was significantly different compared with placebo after four and 12 weeks. There was a significant linear relation between dose and plasma norepinephrine after four and 12 weeks in both 2 h peak and the time averaged effect (>8 h). The number of adverse events was similar in the **moxonidine** and placebo groups. CONCLUSIONS: The increased sympathetic activation in CHF can be reduced by **moxonidine** through CNS inhibition.

L73 ANSWER 20 OF 137 MEDLINE
2000489325 Document Number: 20494299. PubMed ID: 11039256. [Central agents in arterial hypertension: back to the future]. Agentes centrales en hipertension arterial: regreso al futuro. Robles N R. (Unidad de Hipertension Arterial, Hospital Infanta Cristina, Badajoz. ) NEFROLOGIA, (2000 Jul-Aug) 20 (4) 302-10. Ref: 77. Journal code: DLP. ISSN: 0211-6995. Pub. country: Spain. Language: Spanish.

L73 ANSWER 21 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000270188 EMBASE Update on recent clinical trials in congestive **heart failure**. Betkowski A.S.; Hauptman P.J.. Dr. P.J. Hauptman, Division of Cardiology, Saint Louis University, Health Sciences Center, 3635 Vista Avenue at Grand Blvd., St. Louis, MO 63110, United States. hauptmpj@slu.edu. Current Opinion in Cardiology 15/4 (293-303) 2000.
Refs: 86.
ISSN: 0268-4705. CODEN: COPCE3. Pub. Country: United States. Language: English. Summary Language: English.
AB Understanding of the pathophysiology of **heart failure** has advanced over the last decade, resulting in new **therapeutic** advances. Convincing data exist that angiotensin-converting enzyme (ACE) inhibition and adrenergic blockade are the most important **therapies** and have the capacity to improve survival and lower morbidity. Higher doses of both ACE inhibitors and beta-blockers appear to provide additional benefits. The aldosterone antagonist spironolactone, when used in severe **heart failure**, provides additional survival advantage when added to standard triple **therapy**. Angiotensin receptor blockers have not been shown to be superior to ACE inhibitors, and their role in **heart failure** **treatment** requires further investigation. No trial's data support the use of inotropic agents or calcium channel blockers in **heart failure**. A number of new **therapeutic** agents, including vasopressin antagonists and tumor necrosis factor-.alpha. receptor antibody are in phase II and III clinical trials. If proved beneficial, they may provide new **treatment** options for patients with **heart failure**. Nevertheless, the current challenge is to increase the use of proven **therapies**, namely ACE inhibitors and beta-blockers, to improve outcomes in the rapidly growing population of patients with congestive **heart failure**. (C) 2000 Lippincott Williams and Wilkins, Inc.

L73 ANSWER 22 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000310567 EMBASE Importance of neuroendocrine activation in chronic **heart failure**. Impact on **treatment** strategies.
Swedberg K.. K. Swedberg, Department of Medicine, Sahlgrenska Univ. Hospital/Ostra, Goteborg University, SE-41685 Goteborg, Sweden. karl.swedberg@hjl.gu.se. European Journal of Heart Failure 2/3 (229-233) 2000.
Refs: 29.
ISSN: 1388-9842. CODEN: EJHFFS.
Publisher Ident.: S 1388-9842(00)00102-1. Pub. Country: Netherlands.
Language: English.

Searched by: Mary Hale 308-4258 CM-1 12D16

L73 ANSWER 23 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000418096 EMBASE Renewed interest in centrally acting antihypertensive drugs. Van Zwieten P.A.. Dr. P.A. Van Zwieten, Academic Medical Centre, Department of Pharmacotherapy, University of Amsterdam, Amsterdam, Netherlands. Cardiovascular Journal of Southern Africa 11/4 (225-229) 2000.
Refs: 32.
ISSN: 1015-9657. CODEN: CJSAEB. Pub. Country: South Africa. Language: English. Summary Language: English.

AB Classic centrally acting drugs such as clonidine and .alpha.-methyldopa induce peripheral sympatho-inhibition via the stimulation of .alpha.2-adrenoceptors in the brainstem. From a haemodynamic point of view this appears to be a useful mechanism to lower elevated blood pressure in hypertensives. Although not known in full detail, a complex relationship exists between the **sympathetic nervous system** and hypertensive disease; sympathetic inhibition therefore appears to be a logical target of antihypertensive drug **treatment**. Numerous attempts have been made to improve the unfavourable side-effect profile of the centrally acting .alpha.2-adrenoceptor stimulants. None of these attempts were successful, since both the central antihypertensive activity and the major side-effects (sedation, dry mouth) are mediated by .alpha.2-adrenoceptors. A new approach in this field has been offered by the introduction of centrally acting antihypertensives which interact with central imidazoline (I1)-receptors and thus cause peripheral sympatho-inhibition. As such they offer haemodynamic benefits similar to those of the classic .alpha.2-adrenoceptor agonists. However, it is hoped that their side-effect profile will be more favourable because of their much weaker affinity for .alpha.2-adrenoceptors. **Moxonidine** and rilmenidine are the prototypes of centrally acting I1-receptor stimulants. The antihypertensive activity of these agents is caused by vasodilatation and a reduction of peripheral vascular resistance. Left ventricular end-diastolic and end-systolic volumes are reduced, whereas heart rate, stroke volume, cardiac output and pulmonary artery pressures are largely unchanged. Left ventricular hypertrophy (LVH) is reduced in the long term. Both drugs when applied in a once-daily dosage schedule appear to control hypertension in most patients. Both drugs have been compared with representative agents from the major classes of antihypertensives in controlled trials and have been found to be equally effective with respect to blood pressure control. The incidence and severity of side-effects is lower than for clonidine, in particular with respect to sedation. A rebound (withdrawal) phenomenon has so far not been reported for **moxonidine** and rilmenidine. In conclusion, I1-receptor stimulants appear to offer the potential to be developed as centrally acting agents with a better side-effect profile than the classic .alpha.2-adrenoceptor stimulants, but with similar haemodynamic properties.

L73 ANSWER 24 OF 137 MEDLINE DUPLICATE 8
2002061475 Document Number: 21644779. PubMed ID: 11787475. Effects of sympathetic inhibition on exertional dyspnoea, ventilatory and metabolic responses to exercise in normotensive humans. Galloway S D; De Vito G; McClure S; Nimmo M A; McMurray J J. (Department of Sports Studies, University of Stirling, Scotland, UK.. s.d.r.galloway@stir.ac.uk) . CLINICAL SCIENCE, (2000 Sep) 99 (3) 223-30. Journal code: 7905731. ISSN: 0143-5221. Pub. country: England: United Kingdom. Language: English.

AB Augmentation of circulating noradrenaline concentration stimulates ventilation during the initial stages of exercise and this is accompanied by an increased sensation of dyspnoea and exertion. This previous study [Clark, Galloway, MacFarlane, Henderson, Aitchison and McMurray (1997) Eur. Heart J. 18, 1829-1833] suggested a link between dyspnoea, which commonly limits exercise tolerance in **heart failure** patients, and high circulating noradrenaline concentration in these patients. The present study investigated this relationship further using

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sympathetic inhibition. Ten healthy normotensive males performed 10 min of submaximal cycling exercise at approx. 70% of maximal oxygen uptake per min (VO2max) on three occasions one week apart. The first of these sessions was a familiarization session and the other two were experimental study days. On each of the study days, subjects attended the laboratory in the morning after an overnight fast and, following a resting blood sample, were administered placebo or **moxonidine** (0.4 mg) in a double blind cross-over design. After a 90-min absorption period, subjects undertook the exercise task. Blood was drawn, expired gas was analysed breath by breath, blood pressure, heart rate and ratings of perceived dyspnoea and exertion were obtained. **Moxonidine** **treatment** significantly reduced plasma noradrenaline concentration ($P < 0.01$), mean arterial pressure ($P < 0.01$), and blood glycerol concentration ($P < 0.05$), but no differences were observed in heart rate, the ventilatory response to exercise or subjective ratings of dyspnoea and exertion. This study indicates that reducing sympathetic activity does not affect ventilation, perceived dyspnoea or perceived exertion in normotensive males. Therefore it can be concluded that reducing sympathetic activity may not be an appropriate strategy to help reduce perceived dyspnoea.

L73 ANSWER 25 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000192007 EMBASE Clinical trials, **treatment** guidelines and real life: Editorial. Coats A.J.S.. A.J.S. Coats, National Heart and Lung Institute, Imperial College School of Medicine, Royal Brompton Hospital, Sydney St., London, United Kingdom. International Journal of Cardiology 73/3 (205-207) 31 May 2000.
Refs: 14.
ISSN: 0167-5273. CODEN: IJCDD5.
Publisher Ident.: S 0167-5273(00)00287-4. Pub. Country: Ireland. Language: English.

L73 ANSWER 26 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000402591 EMBASE Disagreement between drug effects on autonomic function and mortality: Another unreliable surrogate endpoint in **heart** **failure**?. Van Veldhuisen D.J.. D.J. Van Veldhuisen, Dept. of Cardiology/Thoraxcenter, University Hospital Groningen, PO Box 30.001, 9700 RB Groningen, Netherlands. d.j.van.veldhuisen@thorax.azg.nl. International Journal of Cardiology 75/2-3 (176-177) 15 Sep 2000.
Refs: 10.
ISSN: 0167-5273. CODEN: IJCDD5.
Publisher Ident.: S 0167-5273(00)00318-1. Pub. Country: Ireland. Language: English.

L73 ANSWER 27 OF 137 MEDLINE DUPLICATE 9
2001078633 Document Number: 20530599. PubMed ID: 11077130. The effects of chronic, sustained-release **moxonidine therapy** on clinical and neurohumoral status in patients with **heart** **failure**. Dickstein K; Manhenke C; Aarsland T; McNay J; Wiltse C; Wright T. (Cardiology Division, Central Hospital in Rogaland, 4011, Stavanger, Norway.. trout@online.no) . INTERNATIONAL JOURNAL OF CARDIOLOGY, (2000 Sep 15) 75 (2-3) 167-76; discussion 176-7. Journal code: GQW. ISSN: 0167-5273. Pub. country: Ireland. Language: English.
AB AIMS: Congestive **heart failure** (CHF) is characterized by elevated plasma norepinephrine (PNE) associated with a poor prognosis. **Moxonidine** selectively stimulates medullary imidazoline receptors which centrally inhibit sympathetic outflow and potently suppress levels of circulating PNE. This study was designed to evaluate the effects of central sympathetic inhibition on clinical and neurohumoral status in patients with CHF. METHODS AND RESULTS: This study evaluated 25 patients (age=69+/-7 years, 20 males) with symptomatic CHF (NYHA II-III), stabilized on standard **therapy**. The mean ejection fraction was

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28+/-7% at baseline. Patients were titrated in a double-blind fashion to 11 weeks of oral **therapy** with placebo (n=9) or sustained-release (SR) **moxonidine** 0.9 mg bid (n=16). Clinical and neurohumoral status were evaluated at baseline, on chronic **therapy** at the target dose, and during cessation of **therapy**. All patients completed the trial and reached the target dose. Dry mouth, symptomatic hypotension, and asthenia were more frequent in the **moxonidine** SR-**treated** group. PNE was substantially reduced after 6 weeks at the maximum dose (0.9 mg bid) by 50% vs. placebo (P<0. 0005). A reduction in 24-h mean heart rate (P<0.01) was correlated to the reduction in PNE (r=0.70, P<0.05). A 36% increase in the standard deviation of normal-to-normal intervals (SDNN) was observed in the **moxonidine** SR group vs. a 2% decrease for placebo (P=0.06); for the root mean square of successive differences (rMSSD), there was a 21% increase for **moxonidine** SR vs. a 19% decrease for placebo (P<0.05). Abrupt cessation of chronic **therapy** resulted in substantial increases in PNE, blood pressure, and heart rate. CONCLUSIONS: Chronic **therapy** with a sustained-release formulation of **moxonidine** in patients with CHF was well tolerated, with substantial and sustained reductions in PNE. The tachyarrhythmias were attenuated, with evidence of improved autonomic tone. Due to the observed effects following **moxonidine** discontinuation, tapering of **therapy** is recommended.

L73 ANSWER 28 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:106199 Document No.: PREV200100106199. Differences of leptin levels in hypertensive patients receiving **moxonidine** are associated to a better metabolic control. Sanjuliani, A. (1); Barroso, S. (1); Rodrigues, M. (1); Aquino, K. (1); Duarte, A. (1); Fagundes, V. (1); Francischetti, E. (1). (1) Hypertension Clinic-CLINEX, UERJ, Rio de Janeiro Brazil. Journal of Hypertension, (2000) Vol. 18, No. Suppl. 4, pp. S142. print. Meeting Info.: 18th Scientific Meeting of the International Society of Hypertension Chicago, Illinois, USA August 20-24, 2000 International Society of Hypertension. ISSN: 0263-6352. Language: English. Summary Language: English.

L73 ANSWER 29 OF 137 MEDLINE
2000502082 Document Number: 20503211. PubMed ID: 11048538. [Imidazole receptor agonists--a new advance in the **treatment** of hypertension?]. Agoniste imidazolinovych receptoru--novy pokrok v lecbe hypertenze?. Spinar J; Vitovec J. (II. interni klinika FN U svate Anny, Brno. ) VNITRNI LEKARSTVI, (2000 Feb) 46 (2) 122-5. Journal code: XFY. ISSN: 0042-773X. Pub. country: Czech Republic. Language: Czech.
AB Agonists of I1 imidazolin receptors are a new drug groups which was registered for the **treatment** of hypertension. Their antihypertensive action is comparable with current antihypertensives (hydrochlorothiazide, enalapril, atenolol, nifedipine retard) and causes a drop of the systolic BP by cca 15-20 mm Hg and a drop of the diastolic BP by 10-15 mm Hg with a probable normalization of the blood pressure in cca 60% patients with mild to moderate hypertension. Agonists of I1 imidazoline receptors are suitable in particular for the **treatment** of hypertension associated with metabolic syndrome. Their effect in patients with ischaemic heart disease or after a cerebrovascular attack is not known and despite very promising theoretical prerequisites they are not indicated in patients with chronic **heart failure**.

L73 ANSWER 30 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000161649 EMBASE Beta-blockers - Again, a lesson to us all, especially the research funding community. Coats A.J.S.. A.J.S. Coats, National Heart and Lung Institute, Imperial College School of Medicine, Royal Brompton Hospital, Sydney St., London SW3 6NP, United Kingdom. International Journal of Cardiology 73/2 (103-104) 28 Apr 2000.

Searched by: Mary Hale 308-4258 CM-1 12D16

Refs: 10.
ISSN: 0167-5273. CODEN: IJCDD5.
Publisher Ident.: S 0167-5273(00)00273-4. Pub. Country: Ireland. Language: English.

L73 ANSWER 31 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 10
2000:424642 Document No. 133:308234 The control of adrenergic function in **heart failure**. **Therapeutic** intervention.
Clark, Andrew L.; Cleland, John G. F. (Department of Cardiology, Castle Hill Hospital, Hull, HU16 5JQ, UK). Heart Failure Reviews, 5(1), 101-114 (English) 2000. CODEN: HFREFC. ISSN: 1382-4147. Publisher: Kluwer Academic Publishers.
AB A review is given with 165 refs. Chronic **heart failure** is characterized by excess adrenergic activity that augurs a poor prognosis. The reasons for increased adrenergic activity are complex and incompletely understood. The circumstantial evidence relating increased activity to adverse outcome is powerful, but not yet conclusive. In normal subjects, autonomic control of the circulation is predominantly under the control of sympatho-inhibitory inputs from the arterial and cardiopulmonary baroreceptors, with a small input from the excitatory ergo- and chemo-receptors. In **heart failure**, the situation is reversed, with loss of the restraining input from the baroreceptors and an increase in the excitatory inputs, resulting in excessive adrenergic activity. The circumstantial evidence linking neuroendocrine activation with poor outcome coupled with the clin. success of inhibition of the renin-angiotensin-aldosterone system (RAAS) has long suggested that inhibition of adrenergic activity might be beneficial in **heart failure**. There is a no. of potential ways of achieving this. Improved **treatment** of **heart failure** itself may reduce sympathetic drive. There is an interplay between angiotensin II, aldosterone and the **sympathetic nervous system**, and thus RAAS antagonists, such as angiotensin converting enzyme inhibitors and spironolactone could directly reduce sympathetic activation. Exercise rehabilitation may similarly reduce sympathetic activity. Recently, .beta.-adrenergic receptor antagonists were conclusively shown to improve symptoms, reduce hospitalizations and increase survival. However, the demonstration that central redn. of sympathetic activity with agents such as **moxonidine** increases morbidity and mortality suggests that the authors do not properly understand the role of sympathetic activation in the pathophysiol. of **heart failure**.

L73 ANSWER 32 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000200452 EMBASE Anti-arrhythmic properties of **moxonidine** - Implications for the MOXCON study [2] (multiple letters). Wolk R.; Coats A.J.S.. Dr. R. Wolk, Department of Cardiology, Postgraduate Medical School, Warsaw, Poland. International Journal of Cardiology 74/1 (89-92) 12 Jun 2000.
ISSN: 0167-5273. CODEN: IJCDD5.
Publisher Ident.: S 0167-5273(00)00258-8. Pub. Country: Ireland. Language: English.

L73 ANSWER 33 OF 137 MEDLINE DUPLICATE 11
2001681072 Document Number: 21585730. PubMed ID: 11728244. Imidazoline receptor agonist drugs for **treatment** of systemic hypertension and congestive **heart failure**. Palkhiwala S A; Yu A; Frishman W H. (Department of Medicine, New York Medical College, Westchester Medical Center, Valhalla, NY 10595, USA. ) Heart Dis, (2000 Jan-Feb) 2 (1) 83-92. Journal code: 100887299. ISSN: 1521-737X. Pub. country: United States. Language: English.
AB The imidazoline receptors recently have been discovered to be involved in the central nervous system control of sympathetic outflow. A new class of

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centrally acting antihypertensive agents, the imidazoline receptor agonists (rilmenidine and **moxonidine**), have been developed to control blood pressure effectively without the adverse effects of sedation and mental depression that usually are associated with centrally acting antihypertensive agents. This new generation of centrally acting antihypertensive agents is highly selective for the imidazoline receptor but has a low affinity for alpha(2)-adrenergic receptors. The usefulness of these agents in the **treatment** of congestive **heart failure** has not been demonstrated.

L73 ANSWER 34 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999411016 EMBASE The influence of antihypertensive drug **treatment** on the prevention and regression of left ventricular hypertrophy. Van Zwieten P.A.. P.A. Van Zwieten, Department of Pharmacotherapy, Academic Medical Center, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, Netherlands. Cardiovascular Research 45/1 (82-91) 2000.
Refs: 80.
ISSN: 0008-6363. CODEN: CVREAU.
Publisher Ident.: S 0008-6363(99)00291-6. Pub. Country: Netherlands.
Language: English. Summary Language: English.
AB Left ventricular hypertrophy (LVH) has been recognized as an important cardiovascular risk factor. Hypertensive disease is the most frequent background of LVH and it is generally felt that anti-hypertensive **treatment** should not only lower blood pressure but also cause regression of LVH. In the present survey the patho-physiology of LVH, its measurements and animal models used to study LVH are briefly discussed. Subsequently, the effects of various drugs in animal models and in human hypertensives are reviewed. It has been shown repeatedly that various types of antihypertensive drugs show differential activities on the prevention or regression of LVH. It is not only the lowering of blood pressure which determines the anti-LVH activity, but also the interaction of drugs with neuro-endocrine mechanisms such as the renin-angiotensin-aldosterone system and the **sympathetic nervous system**. Copyright (C) 2000 Elsevier Science B.V.

L73 ANSWER 35 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000192131 EMBASE **Heart failure**: Future **treatment** approaches. Cohn J.N.. Dr. J.N. Cohn, University of Minnesota Medical Sch., 420 Delaware Street E., Minneapolis, MN 55455, United States. American Journal of Hypertension 13/5 II SUPPL. (74S-78S) 2000.
Refs: 25.
ISSN: 0895-7061. CODEN: AJHYE6.
Publisher Ident.: S 0895-7061(99)00271-5. Pub. Country: United States.
Language: English. Summary Language: English.
AB Large-scale clinical trials of vasodilators with nitrates and hydralazine and with angiotensin-converting enzyme (ACE) inhibitors in the 1980s and early 1990s provided the first credible evidence that medical **therapy** can prolong survival in patients with chronic **heart failure** (CHF). Moreover, patients **treated** with ACE inhibitors required fewer hospitalizations for worsening **heart failure** (HF). Nonetheless, the prognosis in patients with HF remains bleak, and better **therapies** are urgently needed. Recently, .beta.-blockers and spironolactone have been shown to reduce mortality when added to ACE inhibitors, diuretics, and digoxin. Digoxin has a neutral effect on overall mortality but does reduce the rate of hospitalization. Angiotensin II receptor blockers (ARB) inhibit the AT1 angiotensin receptor, which mediates the deleterious effects of the renin-angiotensin system, and may provide advantages over ACE inhibitors or advantages when used in combination with ACE inhibitors. Newer drugs that interfere with other mechanisms that contribute to progression of **heart failure** are also under study. As new **therapies** prove effective in large populations, they lead to

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a mandate for polypharmacy. The long-term solution to this clinical problem is to develop sensitive and reliable markers that can predict response in individual patients or monitor effectiveness of **therapy**. (C) 2000 American Journal of Hypertension, Ltd.

L73 ANSWER 36 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000384536 EMBASE [**Heart failure** - Threatening, but **treatable**]. HERZINSUFFIZIENZ - BEDROHLICH, ABER BEHANDELBAR.
Deutsche Apotheker Zeitung 140/42 (71-76) 19 Oct 2000.
ISSN: 0011-9857. CODEN: DAZEA2. Pub. Country: Germany. Language: German.

L73 ANSWER 37 OF 137 MEDLINE
2001250498 Document Number: 21243586. PubMed ID: 11346219.
**Moxonidine**: a new and versatile antihypertensive. Messerli F. (Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, New Orleans, Louisiana 70121, USA. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (2000) 35 (7 Suppl 4) S53-6. Ref: 40.
Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States.
Language: English.
AB Despite a proven efficacy in lowering blood pressure, centrally acting antihypertensive drugs are no longer widely used because of the relative high incidence of adverse effects. Most central side-effects occurring with these drugs are mediated by the alpha2-receptor. **Moxonidine** is an imidazoline receptor agonist that is highly selective for the I1-imidazoline receptor with little effect at the central alpha2-receptor. **Moxonidine** has been shown to diminish sympathetic activity, as measured by norepinephrine, epinephrine and plasma renin activity. Acute and long-term hemodynamic studies show that **moxonidine** reduces arterial pressure by lowering systemic vascular resistance while sparing heart rate, cardiac output and stroke volume. **Moxonidine** has been shown to reduce left ventricular hypertrophy and is metabolically neutral; it may have a favourable effect on insulin resistance. Clinical studies have documented efficacy of **moxonidine** as an antihypertensive agent. Most patients' blood pressure was satisfactorily controlled with a dose between 0.2 and 0.4 mg per day. Comparative studies are available with most other antihypertensive drug classes, such as clonidine, diuretics, alpha-blockers, beta-blockers, calcium antagonists, and ACE inhibitors, and document similar blood pressure control with **moxonidine** as with other agents. Specifically, by using 24-h ambulatory blood pressure monitoring, blood pressure control was found to be similar with **moxonidine** and enalapril. The side-effect profile of **moxonidine** has been shown to be favorable as might be expected from its lack of an alpha2-receptor mediated central effect. **Moxonidine**, therefore, represents an advance in the tolerability of anti-adrenergic drugs without apparent reduction in efficacy. All of these observations suggest that **moxonidine** may offer advantages over other antihypertensive drugs, but clearly these potential advantages need to be properly evaluated in a prospective morbidity and mortality study.

L73 ANSWER 38 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000421836 EMBASE Antihypertensive drugs and the **sympathetic nervous system**. Wenzel R.R.; Bruck H.; Noll G.; Schafers R.F.; Daul A.E.; Philipp T.. Dr. R.R. Wenzel, Div. of Nephrology and Hypertension, University Hospital Essen, Hufelandstrasse 55, D-45122 Essen, Germany. Journal of Cardiovascular Pharmacology 35/SUPPL. 4 (S43-S52) 2000.
Refs: 122.
ISSN: 0160-2446. CODEN: JCPCDT. Pub. Country: United States. Language: English. Summary Language: English.
AB The **sympathetic nervous system** (SNS) plays an important role in the regulation of blood pressure homeostasis and

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cardiac function. Furthermore, the increased SNS activity is a predictor of mortality in patients with hypertension, coronary artery disease and congestive **heart failure**. Experimental data and a few clinical trials suggest that there are important interactions between the main pressor systems, i.e. the SNS, the renin-angiotensin system and the vascular endothelium with the strongest vasoconstrictor, endothelin. The main methods for the assessment of SNS activity are described. Cardiovascular drugs of different classes interfere differently with the SNS and the other pressor systems. Pure vasodilators including nitrates, .alpha.-blockers and dihydropyridine (DHP)-calcium channel blockers increase SNS activity. Finally, central sympatholytics and possibly phenylalkylamine-type calcium channel blockers reduce SNS activity. The effects of angiotensin-II receptor antagonists on SNS activity in humans is not clear; experimental data are discussed in this review. There are important interactions between the pressor systems under experimental conditions. Recent studies in humans suggest that an activation of the SNS with pure vasodilators in parallel increases plasma endothelin. It can be assumed that, in cardiovascular diseases with already enhanced SNS activity, drugs which do not increase SNS activity or even lower it are preferable. Whether this reflects in lower mortality needs to be investigated in intervention trials.

L73 ANSWER 39 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000174713 EMBASE Measurement of **sympathetic nervous system** activity in **heart failure**: The role of norepinephrine kinetics. Esler M.; Kaye D.. Dr. M. Esler, Baker Medical Research Institute, Alfred Lane, Prahran 3181, Melbourne, Vic., Australia. esler@baker.edu.au. Heart Failure Reviews 5/1 (17-25) 2000.
Refs: 47.
ISSN: 1382-4147. CODEN: HFREFC. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB Recent demonstration that the level of sympathetic nervous drive to the failing heart in patients with severe **heart failure** is a major determinant of prognosis, and that mortality in **heart failure** is reduced by beta-adrenergic blockade, indicate the clinical relevance of **heart failure** neuroscience research. The cardiac sympathetic nerves are preferentially stimulated in severe **heart failure**, with the application of isotope dilution methods for measuring cardiac norepinephrine release to plasma indicating that in untreated patients cardiac norepinephrine spillover is increased as much as 50-fold, similar to levels of release seen in the healthy heart during near maximal exercise. This preferential activation of the cardiac sympathetic outflow contributes to arrhythmia development and to progressive deterioration of the myocardium, and has been linked to mortality in both mild and severe cardiac failure. Although the central nervous system mechanisms involved in the sympathetic nervous activation at present remain uncertain, increased intracardiac diastolic pressure seems to be one peripheral reflex stimulus, and increased forebrain norepinephrine turnover an important central mechanism. Additional neurophysiological abnormalities present in the failing human heart include release of the sympathetic cotransmitters, epinephrine and neuropeptide Y, at high levels more typical of their release during exercise in healthy subjects, and the possible presynaptic augmentation of norepinephrine release from the cardiac sympathetic nerves by the regionally released epinephrine. Following on the demonstrable benefit of beta-adrenergic blockade in **heart failure**, additional antiadrenergic measures (central suppression of sympathetic outflow with imidazoline binding agents such as clonidine, blocking of norepinephrine synthesis by dopamine-.beta.-hydroxylase inhibition, antagonism of neuropeptide Y) are now under active investigation.

L73 ANSWER 40 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

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2000032244 EMBASE Will it be a choice between quality or quantity of life for patients with **heart failure**?. Drugs and Therapy Perspectives 15/1 (14-15) 17 Jan 2000.
Refs: 14.
ISSN: 1172-0360. CODEN: DTHPEE. Pub. Country: New Zealand. Language: English.

L73 ANSWER 41 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000345017 EMBASE [Sympathetic nerve system and progression of chronic renal failure]. SYMPATHISCHES NERVENSYSTEM UND PROGRESSION DER CHRONISCHEN NIERENINSUFFIZIENZ. Amann K.; Daum O.; Rump L.-C.; Orth S.R.; Gross M.L.; Buzello M.; Simonaviciene A.; Koch A.; Oberhauser V.; Magener A.; Ritz E.; Mall G.. Dr. K. Amann, Pathologisches Institut, Universitat Erlangen-Nurnberg, Krankenhausstrasse 8-10, D-91054 Erlangen, Germany. kerstin.amann@patho.imed.uni-erlangen.de. Journal fur Hypertonie 4/3 (14-23) 2000.
Refs: 39.
ISSN: 1028-2327. CODEN: JHYPFE. Pub. Country: Austria. Language: German. Summary Language: English; German.
AB In contrast to the renin system, the potential effect of the sympathetic system on progression of renal disease has received little attention. Increased activity of the **sympathetic nervous system** has been described in hypertension as well as in renal failure but its role in the progression of renal insufficiency has not been analysed in greater detail. In order to investigate a potential blood pressure independent effect of sympathetic blockade the effect of a non-antihypertensive dose of the central sympatholytic agent **moxonidine** on structural and functional changes of the kidney were analysed in an experimental model of renal damage, the subtotally nephrectomized rat. In summary, glomerulosclerosis and urinary albumine excretion as structural and functional parameters of renal damage were attenuated by **moxonidine** in a non-hypotensive dose. The data provide indirect evidence that increased sympathetic activity, possibly mediated via afferent signals from the damaged kidneys, contribute to the progression of renal failure. This observation may open new **therapeutic** perspectives.

L73 ANSWER 42 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000113703 EMBASE The importance and complexity of neurohumeral over-activity in chronic **heart failure**. Coats A.J.S.. A.J.S. Coats, Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, Sydney Street, London SW3 6NP, United Kingdom. a.coats@ic.ac.uk. International Journal of Cardiology 73/1 (13-14) 31 Mar 2000.
Refs: 9.
ISSN: 0167-5273. CODEN: IJCDD5.
Publisher Ident.: S 0167-5273(00)00173-X. Pub. Country: Ireland. Language: English.

L73 ANSWER 43 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000084094 EMBASE Inotropes in the beta-blocker era. Lowes B.D.; Simon M.A.; Tsvetkova T.O.; Bristow M.R.. Dr. M.R. Bristow, Division of Cardiology, University of Colorado HSC, 4200 East 9th Avenue, Denver, CO 80262, United States. Clinical Cardiology 23/3 SUPPL. (III11-III16) 2000.
Refs: 48.
ISSN: 0160-9289. CODEN: CLCADC. Pub. Country: United States. Language: English. Summary Language: English.
AB Beta-adrenergic blocking agents are now standard **treatment** for mild to moderate chronic **heart failure** (CHF). However, although many subjects improve on beta blockade, others do not, and some may even deteriorate. Even when subjects improve on beta blockade, they may subsequently decompensate and need acute **treatment** with a

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positive inotropic agent. In the presence of full beta blockade, a beta agonist such as dobutamine may have to be administered at very high (> 10 .mu.g/kg/min) doses to increase cardiac output, and these doses may increase afterload. In contrast, phosphodiesterase inhibitors (PDEIs) such as milrinone or enoximone retain their full hemodynamic effects in the face of beta blockade. This is because the site of PDEI action is beyond the beta-adrenergic receptor, and because beta blockade reverses receptor pathway desensitization changes, which are detrimental to PDEI response. Moreover, when the combination of a PDEI and a beta-blocking agent is administered long term in CHF, their respective efficacies are additive and their adverse effects subtractive. The PDEI is administered first to increase the tolerability of beta-blocker initiation by counteracting the myocardial depressant effect of adrenergic withdrawal. With this combination, the signature effects of beta blockade (a substantial decrease in heart rate and an increase in left ventricular ejection fraction) are observed, the hemodynamic support conferred by the PDEI appears to be sustained, and clinical results are promising. However, large-scale placebo-controlled studies with PDEIs and beta blockers are needed to confirm these results.

L73 ANSWER 44 OF 137 MEDLINE DUPLICATE 12

2001250499 Document Number: 21243581. PubMed ID: 11346220. Insulin resistance in chronic **heart failure**. Coats A J; Anker S D; Anker S. (National Heart and Lung Institute, Imperial College of Science, Technology and Medicine, Royal Brompton Hospital, London, UK. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (2000) 35 (7 Suppl 4) S9-14. Ref: 30. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB Insulin resistance is an important risk factor for the development of hypertension, atherosclerotic heart disease, left ventricular hypertrophy and dysfunction, and **heart failure**. It reflects a disturbance of glucose metabolism and potentially worsens metabolic efficiency of both skeletal muscle and cardiac muscle. The exact mechanisms of insulin resistance are not known, but the finding of significant insulin resistance occurring as a consequence of **heart failure** raises interesting possibilities as to its pathogenesis. While **sympathetic nervous system** overactivity can acutely reduce insulin sensitivity, it is not clear to what extent, in stable optimally **treated** chronic **heart failure** (CHF), the neurohormonal overactivity of this syndrome is the major cause of insulin resistance. Other potential mechanisms include the loss of skeletal muscle bulk, impaired endothelial function and reduced skeletal muscle blood flow, and a possible direct action of proinflammatory cytokines such as tumour necrosis factor-alpha. The consequences of insulin resistance in **heart failure** are not known, but the severity of the abnormality appears to parallel symptomatics and exercise limitation in this condition, and, in particular, be related to the impairment of gross skeletal muscle function. While specific **therapies** to correct insulin resistance in CHF have not been evaluated, there are several exciting possibilities on the horizon. Several nonpharmacological **therapies** have been shown to increase insulin sensitivity in patients with normal left ventricular function, and if these benefits could be duplicated in CHF, they may offer symptomatic benefit. These include weight reduction in the obese, regular exercise training and the use of dietary manipulation such as low-fat, high-fibre diets. Drug **treatments** with positive effects on insulin sensitivity include some angiotensin converting enzyme-inhibitors as well as newer drug groups, such as the glitazones and **moxonidine**, a centrally active agent with effects on the recently described imidazoline I-1 receptor that inhibits central sympathetic tone. The role of these agents in reversing the insulin resistance of chronic **heart failure** warrants further investigation.

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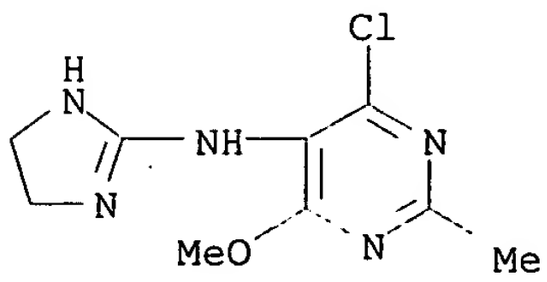
L73 ANSWER 45 OF 137 CAPLUS COPYRIGHT 2002 ACS
2000:831782 Document No. 134:69435 Insulin resistance in chronic **heart failure**. Coats, Andrew J. S.; Anker, Stefan (National Heart and Lung Institute, Imperial College of Science, Technology and Medicine, London, SW3 6NP, UK). Journal of Cardiovascular Pharmacology, 35(Suppl. 4), S9-S14 (English) 2000. CODEN: JCPCDT. ISSN: 0160-2446. Publisher: Lippincott Williams & Wilkins.

AB A review, with 30 refs. Insulin resistance is an important risk factor for the development of hypertension, atherosclerotic heart disease, left ventricular hypertrophy and dysfunction, and **heart failure**. It reflects a disturbance of glucose metab. and potentially worsens metabolic efficiency of both skeletal muscle and cardiac muscle. The exact mechanisms of insulin resistance are not known, but the finding of significant insulin resistance occurring as a consequence of **heart failure** raises interesting possibilities as to its pathogenesis. While **sympathetic nervous system** overactivity can acutely reduce insulin sensitivity, it is not clear to what extent, in stable optimally **treated** chronic **heart failure** (CHF), the neurohormonal overactivity of this syndrome is the major cause of insulin resistance. Other potential mechanisms include the loss of skeletal muscle bulk, impaired endothelial function and reduced skeletal muscle blood flow, and a possible direct action of proinflammatory cytokines such as tumor necrosis factor-alpha. The consequences of insulin resistance in **heart failure** are not known, but the severity of the abnormality appears to parallel symptomatics and exercise limitation in this condition, and, in particular, be related to the impairment of gross skeletal muscle function. While specific **therapies** to correct insulin resistance in CHF have not been evaluated, there are several exciting possibilities on the horizon. Several non-pharmacol. **therapies** have been shown to increase insulin sensitivity in patients with normal left ventricular function, and if these benefits could be duplicated in CHF, they may offer symptomatic benefit. These include wt. redn. in the obese, regular exercise training and the use of dietary manipulation such as low-fat, high-fiber diets. Drug **treatments** with pos. effects on insulin sensitivity include some angiotensin converting enzyme-inhibitors as well as newer drug groups, such as the glitazones and **moxonidine**, a centrally active agent with effects on the recently described imidazoline I-1 receptor that inhibits central sympathetic tone. The role of these agents in reversing the insulin resistance of chronic **heart failure** warrants further investigation.

IT **75438-57-2, Moxonidine**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(insulin resistance in chronic **heart failure**)

RN 75438-57-2 CAPLUS
CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)

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L73 ANSWER 46 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000377256 EMBASE Electrical stimulation of the failing heart: A new **therapeutical** strategy?. Tavazzi L.. Dr. L. Tavazzi, IRCCS Policlinico San Matteo, Divisione di Cardiologia, P. le Golgi 2, 27100 Pavia, Italy. European Heart Journal, Supplement 2/J (J2-J5) 2000.
Refs: 5.
ISSN: 1520-765X. CODEN: EHJSFT. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Only neurohormonal modulating drugs have been shown to be effective in chronic **heart failure**; no drugs with a primary cardiovascular action survived the challenge of mortality studies. Electrical ventricular stimulation, by inducing a better ventricular contraction synergy, might be the first **therapy** of **heart failure** acting exclusively on the heart. However, this new **therapeutical** strategy also has to be validated in morbidity-mortality studies, which are ongoing. In the meantime observational studies have been performed to outline the clinical profile, to optimize the technical characteristics and to explore the feasibility of this new **heart failure treatment**. The InSync Italian Registry is one of them; the mean results of this multicentre investigation are reported in this Supplement. From the analysis of the findings of both observational and controlled randomized trials, two main questions need to be answered: whether ventricular stimulation is effective and safe in large populations of **heart failure** patients and which patients are candidates for resynchronization **therapy**. Within a few years the answers will be available to the medical community. (C) 2000 The European Society of Cardiology.

L73 ANSWER 47 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000421831 EMBASE **Sympathetic nervous system** activation in essential hypertension, cardiac failure and psychosomatic heart disease. Esler M.; Kaye D.. Prof. M. Esler, Baker Medical Research Institute, Alfred Lane, Prahran, Vic. 3181, Australia. Journal of Cardiovascular Pharmacology 35/SUPPL. 4 (S1-S7) 2000.
Refs: 44.
ISSN: 0160-2446. CODEN: JCPCDT. Pub. Country: United States. Language: English. Summary Language: English.

AB Regional sympathetic activity can be studied in humans using electrophysiological methods measuring sympathetic nerve firing rates and neurochemical techniques providing quantification of noradrenaline spillover to plasma from sympathetic nerves in individual organs. Essential hypertension: Such measurements in patients with essential hypertension disclose activation of the sympathetic outflows to skeletal muscle blood vessels, the heart and kidneys, particularly in younger patients. This sympathetic activation, in addition to underpinning the blood pressure elevation, most likely also contributes to left ventricular hypertrophy, and to the commonly associated metabolic abnormalities of insulin resistance and hyperlipidaemia. Antihypertensive drugs, such as **moxonidine**, which act primarily by inhibiting the **sympathetic nervous system**, should have additional clinical benefits beyond those attributable to blood pressure reduction, in protecting against hypertensive complications. Obesity-related hypertension: Understanding the neural pathophysiology of hypertension in the obese has been difficult. In normotensive obesity, renal sympathetic tone is doubled, but cardiac noradrenaline spillover (a measure of sympathetic activity in the heart) is only 50% of normal. In obesity-related hypertension, there is a comparable elevation of renal noradrenaline spillover, but without suppression of cardiac sympathetics (cardiac sympathetic activity being more than double that of normotensive obese and 25% higher than in healthy volunteers). Increased renal sympathetic activity in obesity may be a 'necessary' cause for the

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development of hypertension (and predisposes to hypertension development), but apparently is not a 'sufficient' cause. The discriminating feature of the obese who develop hypertension is the absence of the adaptive suppression of cardiac sympathetic tone seen in the normotensive obese. **Heart failure**: In cardiac failure, the sympathetic nerves of the heart are preferentially stimulated. Noradrenaline release from the failing heart at rest in untreated patients is increased as much as 50-fold, similar to the level seen in the healthy heart during near-maximal exercise. Activation of the cardiac sympathetic outflow provides adrenergic support to the failing myocardium, but at a cost of arrhythmia development and progressive myocardial deterioration. Psychosomatic heart disease: No more than 50% of clinical coronary heart disease is explicable in terms of classical cardiac risk factors. There is gathering evidence that psychological abnormalities, particularly depressive illness, anxiety states, including panic disorder and mental stress, are involved here, 'triggering' clinical cardiovascular events, and possibly also contributing to atherosclerosis development. The mechanisms of increased cardiac risk attributable to mental stress and psychiatric illness are not entirely clear, but activation of the **sympathetic nervous system** seems to be of prime importance.

L73 ANSWER 48 OF 137 MEDLINE
2000039550 Document Number: 20039550. PubMed ID: 10574393. **Heart Failure** 99 -- the MOXCON story. Coats A J. INTERNATIONAL JOURNAL OF CARDIOLOGY, (1999 Oct 31) 71 (2) 109-11. Journal code: GQW; 8200291. ISSN: 0167-5273. Pub. country: Ireland. Language: English.

L73 ANSWER 49 OF 137 MEDLINE
2000071320 Document Number: 20071320. PubMed ID: 10603665. [New central agents in the **treatment** of arterial hypertension]. Nuevos agentes centrales en el tratamiento de la hipertension arterial. Robles N R. ANALES DE MEDICINA INTERNA, (1999 Oct) 16 (10) 495-7. Journal code: A5E; 9112183. ISSN: 0212-7199. Pub. country: Spain. Language: Spanish.

L73 ANSWER 50 OF 137 CAPLUS COPYRIGHT 2002 ACS
1999:184138 Document No. 130:209719 Preparation of imidazolidinylideneaminopyrimidines for **treatment** of hypertension, congestive **heart failure**, atherosclerosis, drug withdrawal, and non-insulin dependent diabetes.. Abraham, Trent Lee; Czeskis, Boris Arnoldovich; He, Minxia; Shipley, Lisa Ann (Eli Lilly and Company, USA). PCT Int. Appl. WO 9911269 A1 19990311, 29 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US18381 19980903. PRIORITY: US 1997-57472 19970903.
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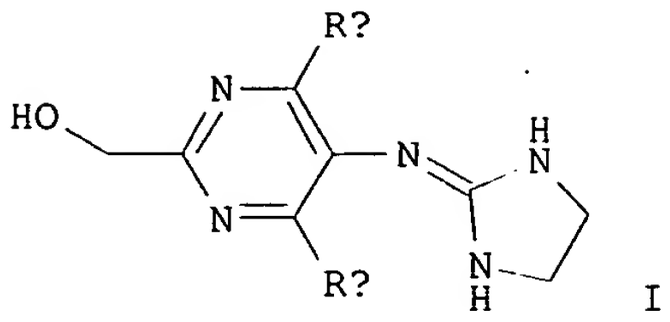

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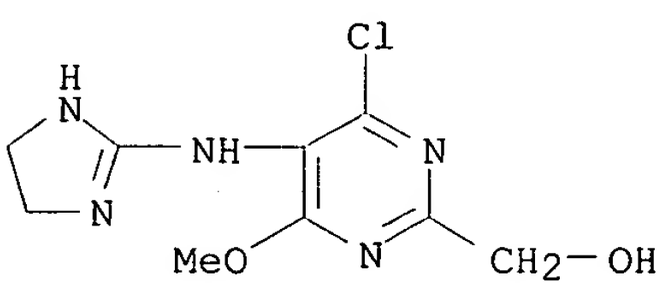
AB Title compds. (I; Ra, Rb = halo, alkoxy), and esters or amides thereof, were prepd. Thus, hydroxyacetamidine hydrochloride was stirred 5 min. in EtOH contg. NaOEt; Et malonate was added and the mixt. was refluxed 3 h to give 79% 4,6-dihydroxy-2-hydroxymethylpyrimidine. This was stirred with fuming HNO3/AcOH to give 80.5% 4,6-dihydroxy-2-hydroxymethyl-5-nitropyrimidine, which was heated with AcOH/Ac2O at 105.degree. for 2 h to give 99% 2-acetoxymethyl-4,6-dihydroxy-5-nitropyrimidine. The latter was refluxed 2 h with POCl3 and PhNEt2 to give 77% 2-acetoxymethyl-4,6-dichloro-5-nitropyrimidine, which was hydrogenated in EtOH over Raney Ni to give 89% 2-acetoxymethyl-4,6-dichloro-5-aminopyrimidine. **Treatment** of the amine with N-acetyl-2-imidazolidone and POCl3 at 105-110.degree. for 3 h gave 59% 2-acetoxymethyl-4,6-dichloro-5-(1-acetylimidazolidin-2-ylidenimino)pyrimidine. The latter was refluxed with NaOMe in MeOH to give 50% 2-hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxypyrimidine. The latter reduced blood pressure and heart rate in rats.

IT **220951-60-0P**, 2-Hydroxymethyl-4-chloro-5-(imidazolidin-2-ylidenimino)-6-methoxypyrimidine
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazolidinylideneaminopyrimidines for **treatment** of hypertension, congestive **heart failure**, atherosclerosis, drug withdrawal, and non-insulin dependent diabetes)

RN 220951-60-0 CAPLUS

CN 2-Pyrimidinemethanol, 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)amino]-6-methoxy- (9CI) (CA INDEX NAME)



L73 ANSWER 51 OF 137 MEDLINE DUPLICATE 13

1999320039 Document Number: 99320039. PubMed ID: 10392868. Acute hemodynamic and neurohumoral effects of **moxonidine** in congestive **heart failure** secondary to ischemic or idiopathic dilated cardiomyopathy. Dickstein K; Manhenke C; Aarsland T; Kopp U; McNay J; Wiltse C. (Cardiology Division, Central Hospital in Rogaland, and Hjertelaget Research Foundation, Stavanger, Norway.. trout@online.no) . AMERICAN JOURNAL OF CARDIOLOGY, (1999 Jun 15) 83 (12) 1638-44. Journal code: 3DQ; 0207277. ISSN: 0002-9149. Pub. country: United States. Language: English.

AB Elevated plasma norepinephrine (PNE) has been shown to be an important predictor of morbidity and mortality in patients with congestive **heart failure** (CHF). **Moxonidine** selectively

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stimulates imidazoline receptors located in the medulla, which centrally inhibit sympathetic outflow. PNE is suppressed and peripheral vasodilation reduces systemic blood pressure. This study evaluated the acute neurohumoral and hemodynamic effects of a single dose of oral **moxonidine** in 32 patients (22 men, mean +/- SD age 66 +/- 10 years) with CHF. All patients were in New York Heart Association functional class III and stabilized on chronic **therapy** with diuretics, digitalis, and angiotensin-converting enzyme inhibitors. The mean PNE concentration was 509 +/- 304 pg/ml at baseline. Patients underwent invasive hemodynamic monitoring after double-blind randomization to either placebo (n = 12), **moxonidine** 0.4 mg (n = 9), or **moxonidine** 0.6 mg (n = 11). **Moxonidine** produced a dose-dependent, vasodilator response compared with placebo. Analysis of the time-averaged change from baseline over 6 hours demonstrated that **moxonidine** 0.6 mg caused significant reductions in mean systemic arterial pressure ($p < 0.0001$), mean pulmonary arterial pressure ($p < 0.005$), systemic vascular resistance ($p < 0.05$), pulmonary vascular resistance ($p < 0.01$), and heart rate ($p < 0.05$). Stroke volume was unchanged. PNE was reduced substantially (-180 pg/ml at 4 hours, $p < 0.005$) and the reduction was highly correlated with the baseline level ($r = -0.968$). **Moxonidine** was well tolerated in this single-dose study and resulted in a modest, dose-dependent, vasodilator response, with substantial reductions in systemic and pulmonary arterial blood pressure. Trials designed to evaluate the clinical efficacy of chronic **moxonidine therapy** in CHF added to conventional **therapy** would be appropriate.

L73 ANSWER 52 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999395134 EMBASE 21st Congress of the European Society of Cardiology, Barcelona, Spain, 27 August to 1 September 1999: Hotline sessions. Verheugt F.W.A.. F.W.A. Verheugt, Heartcenter, University Hospital, Nijmegen, Netherlands. European Heart Journal 20/22 (1603-1606) 1999. Refs: 0.
ISSN: 0195-668X. CODEN: EHJODF. Pub. Country: United Kingdom. Language: English.

L73 ANSWER 53 OF 137 MEDLINE DUPLICATE 14
1999349971 Document Number: 99349971. PubMed ID: 10423108. Centrally acting antihypertensive drugs. Present and future. van Zwieten P A. (Department of Pharmacotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands. ) CLINICAL AND EXPERIMENTAL HYPERTENSION, (1999 Jul-Aug) 21 (5-6) 859-73. Ref: 29. Journal code: BP0; 9305929.
ISSN: 1064-1963. Pub. country: United States. Language: English.
AB The classic centrally acting antihypertensives such as clonidine, guanfacine and alpha-methyl-DOPA (via its active metabolite alpha-methyl-noradrenaline) induce peripheral sympathoinhibition and a fall in blood pressure as a result of alpha2-adrenoceptor stimulation in the brain stem. These drugs have lost much of their clinical importance because of their unfavourable side-effects (sedation, dry mouth, impotence), which are also mediated by alpha2-adrenoceptors, although in other anatomical regions. **Moxonidine** and rilmenidine are the examples of a new class of centrally acting antihypertensives, which cause peripheral sympathoinhibition mediated by imidazoline (I1)-receptors in the rostral ventromedulla (RVLM). Their side-effect profile appears to be better than that of clonidine and alpha-methyl-DOPA, probably because of a weaker affinity for alpha2-adrenoceptors. The mode of action, haemodynamic profile, antihypertensive efficacy and adverse reactions of the classic and newer centrally acting antihypertensives are the subject of the present survey. Attention is also paid to other **therapeutic** applications of centrally acting antihypertensives, such as congestive **heart failure** and the metabolic syndrome.

Searched by: Mary Hale 308-4258 CM-1 12D16

L73 ANSWER 54 OF 137 MEDLINE DUPLICATE 15
2000061310 Document Number: 20061310. PubMed ID: 10595861. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure control and their potential interest in cardioprotection. Bousquet P; Feldman J. (Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Universite Louis Pasteur, Strasbourg, France.. Pascal.Bousquet@medecine.u-strasbg.fr) . DRUGS, (1999 Nov) 58 (5) 799-812. Ref: 110. Journal code: EC2; 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB Drugs acting within the autonomic nervous system are of particular interest when autonomic abnormalities are implicated in the development and maintenance of various cardiovascular pathologies. For example, it has been documented that in the early stages of hypertensive disease, i.e. hyperkinetic borderline hypertension, a sympathetic hyperactivity associated with a decreased parasympathetic activity results in increased cardiac output and heart rate. Several classes of drugs acting within the central, as well as the peripheral, autonomic nervous system are very efficient in **treating** hypertensive disease. One class - the second generation of a group of centrally acting drugs selective for imidazoline receptors - has proved beneficial in this respect, because drugs in this class are well tolerated and have interesting additional effects such as their antiarrhythmic action. Rilmenidine and **moxonidine** are the lead compounds of this class of drugs. Rilmenidine and **moxonidine** both proved more selective for cerebral imidazoline receptors than the reference drug, clonidine. It was suggested that this selectivity, attributable to their lower affinity for alpha2-adrenoceptors, explains the low incidence of adverse effects (including sedation) associated with these drugs. In addition, potentially beneficial actions on cardiac dysrythmias and congestive **heart failure** enlarge the **therapeutic** potential of the second generation of imidazoline-related drugs. This review focuses on the main pharmacological and clinical properties of rilmenidine and **moxonidine**, paying particular attention not only to their efficacy in hypertension but also to other potential cardiovascular indications.

L73 ANSWER 55 OF 137 MEDLINE DUPLICATE 16
2000047301 Document Number: 20047301. PubMed ID: 10578224. The effect of **moxonidine** on plasma lipid profile and on LDL subclass distribution. Elisaf M S; Petris C; Bairaktari E; Karabina S A; Tzallas C; Tselepis A; Siamopoulos K C. (Department of Internal Medicine, University of Ioannina Medical School, Greece. ) JOURNAL OF HUMAN HYPERTENSION, (1999 Nov) 13 (11) 781-5. Journal code: JYT; 8811625. ISSN: 0950-9240. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Moxonidine** is a new antihypertensive agent whose mechanism of action appears to involve specific stimulation of imidazoline receptors resulting in an inhibition of the activity of the central and peripheral **sympathetic nervous system**. The drug seems to behave neutrally with respect to plasma lipid parameters. However, there are no data on the effects of **moxonidine** on the low-density lipoprotein (LDL) subclass pattern or on the LDL oxidation susceptibility, both of which are known to play a prominent role in the pathogenesis of atherosclerosis. Thus, we undertook the present study to examine the influence of **moxonidine** on the LDL subspecies profile and their susceptibility to copper-induced oxidative modification in 20 hypertensive patients (11 men, 9 women) aged 38-61 years. **Moxonidine** administered at a dose of 0.4 mg daily for 8 weeks produced a significant decrease in both systolic and diastolic blood pressure (from 147 +/- 10 to 131 +/- 11 mm Hg, $P < 0.001$, and from 98 +/- 4.5 to 86 +/- 5 mm Hg, $P < 0.001$, respectively). No significant change in plasma lipid profile was observed after **moxonidine** administration. Additionally, no change in the susceptibility of LDL subclasses to copper-induced oxidative modification was noticed. Finally, drug **therapy** was not followed

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by any change in either LDL phenotype or in mass and composition of the three LDL subfractions. We conclude, that unlike other antihypertensive drugs, such as beta-blockers which may predispose to expression of a relatively atherogenic lipoprotein subclass pattern, **moxonidine** does not affect either plasma lipid parameters or lipoprotein composition.

L73 ANSWER 56 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999424631 EMBASE Progress in interventional cardiology. Joseph J.; Saucedo J.; Talley J.D.. Dr. J. Joseph, Internal Medicin, Heart Failure Treatment Program, Univ. of Arkansas for Med. Sciences, Fayetteville, AR, United States. Journal of Interventional Cardiology 12/6 (521-524) 1999.
Refs: 10.
ISSN: 0896-4327. CODEN: JICAF2. Pub. Country: United States. Language: English.

L73 ANSWER 57 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999339255 EMBASE Hypertension. (4): Recent advances in hypertension. Spencer C.; Lip G.. Dr. C. Spencer, University Department of Medicine, City Hospital, Birmingham, United Kingdom. Pharmaceutical Journal 263/7064 (486-488) 25 Sep 1999.
Refs: 19.
ISSN: 0031-6873. CODEN: PHJOAV. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The final article in our series on hypertension and its **treatment** looks at advances in the understanding of the **treatment** of hypertension. Highlights from the recently updated British Hypertension Society guidelines are also included.

L73 ANSWER 58 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000088807 EMBASE Meeting report - The LIDO, HOPE, MOXCON and WASH studies. Jones C.G.; Cleland J.G.F.. C.G. Jones, Cardio.net Editorial Office, King Edward Street, Macclesfield, Cheshire SK10 1AA, United Kingdom. poter@medschool.hull.ac.uk. European Journal of Heart Failure 1/4 (425-431) 1999.
Refs: 4.
ISSN: 1388-9842. CODEN: EJHFFS.
Publisher Ident.: S 1388-9842(99)00059-8. Pub. Country: Netherlands. Language: English. Summary Language: English.
AB This is a summary of the meeting reports of the LIDO, HOPE, MOXCON and WASH studies based on their presentations at recent international symposia. These studies have already been covered, alongside others, as part of the Cardio.net overnight reporting series (www.cardio.net) from these symposia. (C) 1999 European Society of Cardiology.

L73 ANSWER 59 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999281540 EMBASE Recent progress in the **treatment** of hypertension and related disorders. Cases A.. Dr. A. Cases, Dept. of Nephrology, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain. Drug News and Perspectives 12/6 (372-377) 1999.
ISSN: 0214-0934. CODEN: DNPEED. Pub. Country: Spain. Language: English. Summary Language: English.
AB The 14th Annual Scientific Meeting of the American Society of Hypertension, held in New York, May 19-22, 1999, presented recent advances in the field of hypertension and related cardiovascular disorders. Presenters discussed the evidence for the beneficial effects of the use of .beta.-blockers in terms of mortality in patients with **heart failure**. The possible usefulness of endothelin antagonists in hypertension and **heart failure** was also discussed. The overall results of three phase II trials on the antihypertensive efficacy and tolerability of the dual vasopeptidase inhibitor omapatrilat were presented during the meeting. The antihypertensive effects and tolerability of members of the new class of I1 imidazoline receptor

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agonists (rilmenidine and **moxonidine**) were reviewed in a satellite symposium and an invited lecture. The beneficial use of antialdosteronic agents, such as spironolactone, in patients with severe **heart failure** and the recent development of more selective aldosterone receptor antagonists (SARAs), such as eplerenone - currently under investigation in hypertension and **heart failure** - were also presented during the meeting.

L73 ANSWER 60 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:463233 Document No.: PREV199900463233. The effects of chronic, sustained-release **moxonidine therapy** on clinical and neurohumoral status in patients with **heart failure**.
Dickstein, Kenneth (1); Manhenke, Cord (1); Aarsland, Torbjorn; McNay, John; Wiltse, Curtis; Wright, Theressa. (1) Cardiology Division, Central Hospital in Rogaland, Stavanger Norway. European Heart Journal, (Aug., 1999) Vol. 20, No. ABSTR. SUPPL., pp. 322. Meeting Info.: XXIst Congress of the European Society of Cardiology Barcelona, Spain August 28-September 1, 1999 European Society of Cardiology. ISSN: 0195-668X. Language: English.

L73 ANSWER 61 OF 137 MEDLINE
2001150881 Document Number: 21117277. PubMed ID: 11225647. Metabolic effects of **moxonidine** and other centrally acting antihypertensives. Schachter M. (Department of Clinical Pharmacology and Therapeutics, Imperial College School of Medicine, St Mary's Hospital, London, UK.. M.Schachter@ic.ac.uk) . DIABETES, OBESITY & METABOLISM, (1999 Nov) 1 (6) 317-22. Ref: 26. Journal code: DW9; 100883645. ISSN: 1462-8902. Pub. country: England: United Kingdom. Language: English.

L73 ANSWER 62 OF 137 MEDLINE
2001010607 Document Number: 20440467. PubMed ID: 10981082. Centrally acting antihypertensive drugs: re-emergence of sympathetic inhibition in the **treatment** of hypertension. Benedict C R. (University of Texas Medical School, Division of Cardiology, 6431 Fannin Street, MSB 6.039, Houston, Texas 77030, USA. ) CURRENT HYPERTENSION REPORTS, (1999 Aug) 1 (4) 305-12. Ref: 52. Journal code: DTH. ISSN: 1522-6417. Pub. country: United States. Language: English.
AB Central regulation of the **sympathetic nervous system** plays an important role in the maintenance of blood pressure. In a subset of patients with essential hypertension, sympathetic activation may contribute to the development and maintenance of hypertension. Unlike the first generation of centrally active antihypertensive drugs, the second generation may be superior because of its selectivity to I1-imidazoline receptor and selective binding to the vasomotor center. Lack of a2 effects differentiates **moxonidine** from clonidine with respect to monoxidine"s superior side-effect profile (little or no sedation or dry mouth). Clinical trials show that **moxonidine** is as effective as angiotensin-converting enzyme inhibitors (eg, enalapril and captopril), b-blockers (e.g., atenolol), calcium-channel blockers (e.g., long-acting nifedipine), and diuretics (eg, hydrochlorothiazide) in lowering blood pressure and that it has superior tolerability. Thus, central modulation of the **sympathetic nervous system** has re-emerged as an exciting target for blood pressure reduction. Given the multiple adverse effects of sympathetic stimulation in various disease processes, including congestive **heart failure, moxonidine** may be the next **therapeutic** option for the management of hypertension and the prevention of target organ dysfunction.

L73 ANSWER 63 OF 137 MEDLINE
1999344415 Document Number: 99344415. PubMed ID: 10415926. Central imidazoline- and alpha 2-receptors involved in the cardiovascular actions

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of centrally acting antihypertensive agents. Head G A. (Neuropharmacology Laboratory, Baker Medical Research Institute, Prahran, Victoria, Australia.. Geoff.Head@baker.edu.au) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1999 Jun 21) 881 279-86. Journal code: 5NM; 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB There has been a continuing and yet unresolved debate concerning the existence and contribution of imidazoline receptors to the antihypertensive actions of clonidine-like agents. Studies from our laboratory have examined the importance of imidazoline receptors and alpha 2-adrenoceptors in the mechanism of action of centrally acting antihypertensive drugs. We used conscious rabbits and imidazoline and specific alpha 2-adrenoceptor antagonists to show that second-generation agents rilmenidine and **moxonidine** act preferentially through imidazoline receptors but that alpha 2-adrenoceptors are important for the hypotension produced by clonidine and alpha-methyldopa. Using microinjections of the imidazoline antagonists into the rostral ventrolateral medulla (RVLM) of anesthetized rabbits we confirmed the generally held view that this is the major site of sympathoinhibitory actions of centrally acting antihypertensive agents. However, we also found that alpha 2-adrenoceptors are present in this nucleus and appear to be activated as a consequence of imidazoline receptor activation. In recent studies using a noradrenergic neurotoxin microinjected into the RVLM we found that this **treatment** selectively blocked the actions of **moxonidine** but did not affect the level of imidazole proteins, suggesting that I1-imidazoline receptors may be located presynaptic to the noradrenergic terminal. By contrast, clonidine acts directly on the alpha 2-adrenoceptors perhaps located on cell bodies in the nucleus. In conclusion, our studies suggest that imidazoline receptors and alpha 2-adrenoceptors within the RVLM are important for the antihypertensive actions of clonidine-like drugs.

L73 ANSWER 64 OF 137 MEDLINE DUPLICATE 17

2000301485 Document Number: 20301485. PubMed ID: 10842668. Molecular pathology in the obese spontaneous hypertensive Koletsky rat: a model of syndrome X. Ernsberger P; Koletsky R J; Friedman J E. (Department of Nutrition, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106-4935, USA. ) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1999 Nov 18) 892 272-88. Journal code: 5NM; 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The SHROB rat is a unique strain with genetic obesity, hypertriglyceridemia, hyperinsulinemia, renal disease with proteinuria, and genetically determined hypertension, characteristics paralleling human Syndrome X. The obese phenotype results from a single homozygous recessive trait, designated faK, and is allelic with the Zucker fatty trait (fa), but of distinct origin. The faK mutation is a premature stop codon in the extracellular domain of the leptin receptor, resulting in a natural receptor knockout. The SHROB are glucose intolerant compared to heterozygous or wild-type SHR, but retain fasting euglycemia even on a high sucrose diet, suggesting that diabetes requires polygenic interaction with additional modifier genes. Insulin-stimulated phosphorylation of tyrosine residues on the insulin receptor and on the associated docking protein IRS-1 are reduced in skeletal muscle and liver compared to SHR, due mainly to diminished expression of insulin receptor and IRS-1 proteins. Despite multiple metabolic derangements and severe insulin resistance, hypertension is not exacerbated in SHROB compared to SHR. Thus, insulin resistance and hypertension are independent in this model. Increased activity of the **sympathetic nervous system** may be a common factor leading by separate pathways to hypertension and to insulin resistance. We studied the chronic effects of sympathetic inhibition with **moxonidine** on glucose metabolism in SHROB. **Moxonidine** (8 mg/kg/day), a selective I1-imidazoline receptor agonist, not only reduced blood pressure but also ameliorated

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glucose intolerance. **Moxonidine** reduced fasting insulin by 47% and plasma free fatty acids by 30%. **Moxonidine** enhanced expression and insulin-stimulated phosphorylation of IRS-1 in skeletal muscle by 74 and 27%, respectively. Thus, central sympatholytic **therapy** not only counters hypertension but also insulin resistance, glucose tolerance, and hyperlipidemia in the SHROB model of Syndrome X.

L73 ANSWER 65 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:419811 Document No.: PREV199900419811. Chronic **moxonidine** **therapy** produces sustained reduction of plasma norepinephrine in patients with **heart failure**. Dickstein, Kenneth (1); Manhenke, Cord (1); Aarsland, Torbjorn (1); McNay, John (1); Wiltse, Curtis (1); Wright, Theressa (1). (1) Cardiology Division, Central Hospital in Rogaland, Stavanger Norway. Journal of the American College of Cardiology, (Feb., 1999) Vol. 33, No. 2 SUPPL. A, pp. 184A. Meeting Info.: 48th Annual Scientific Session of the American College of Cardiology New Orleans, Louisiana, USA March 7-10, 1999 American College of Cardiology. ISSN: 0735-1097. Language: English.

L73 ANSWER 66 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:419810 Document No.: PREV199900419810. beta-Blockers for Chagas's heart disease: The reduction in heart rate may not be associated to improvement in left ventricular ejection fraction and remodeling process. Freitas, Humberto (1); Salatino, Gustavo (1); Chizzola, Paulo (1); Costa, Joyceli (1); Mansur, Alfredo (1); Ramires, Jose F. (1); Bocchi, Edimar (1). (1) Heart Institute, Sao Paulo Brazil. Journal of the American College of Cardiology, (Feb., 1999) Vol. 33, No. 2 SUPPL. A, pp. 184A. Meeting Info.: 48th Annual Scientific Session of the American College of Cardiology New Orleans, Louisiana, USA March 7-10, 1999 American College of Cardiology. ISSN: 0735-1097. Language: English.

L73 ANSWER 67 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999057627 EMBASE 7th WHO-ISH Meeting on Hypertension, Fukuoka, Japan, 29 September to October, 1998: 1999 World Health Organization - International Society of Hypertension Guidelines for the Management of Hypertension. Alderman M.; Arakawa K.; Beilin L.; Chalmers J.; Erdine S.; Fujishima M.; Hamet P.; Hannson L.; Landsberg L.; Leenen F.; Lindholm L.; Lisheng L.; Mabadeje A.F.B.; MacMahon S.; Mancia G.; Martin I.; Mimran A.; Rahn K.-H.; Ribeiro A.; Sleight P.; Whitworth J.; Zanchetti A.; Neal B.; Rodgers A.; Mhurchu C.N.; Clark T.. Prof. J. Chalmers, Northern Sydney Health, Vindin House, Royal North Shore Hospital, St Leonards, NSW 2065, Australia. jchalmers@med.usyd.edu.au. Journal of Hypertension 17/2 (151-183) 1999. Refs: 199.
ISSN: 0263-6352. CODEN: JOHYD3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

L73 ANSWER 68 OF 137 MEDLINE DUPLICATE 18
1999108003 Document Number: 99108003. PubMed ID: 9862764. Mechanisms of antihyperglycemic effects of **moxonidine** in the obese spontaneously hypertensive Koletsky rat (SHROB). Ernsberger P; Ishizuka T; Liu S; Farrell C J; Bedol D; Koletsky R J; Friedman J E. (Department of Medicine, Division of Hypertension, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA. ) JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1999 Jan) 288 (1) 139-47. Journal code: JP3; 0376362. ISSN: 0022-3565. Pub. country: United States. Language: English.
AB Increased activity of the **sympathetic nervous** **system** may be a critical factor in the development of impaired insulin secretion and insulin resistance. We studied the chronic effects of sympathetic inhibition with **moxonidine** on glucose metabolism in the spontaneously hypertensive genetically obese rat (SHROB). This unique animal model closely resembles human syndrome X, expressing insulin

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resistance, genetic obesity, spontaneous hypertension, and hyperlipoproteinemia. **Moxonidine**, a selective imidazoline receptor agonist, was administered to lean spontaneous hypertensive rats (SHR) and SHROBs for 90 days in food at 8 mg/kg/day and significantly reduced mean blood pressure. **Moxonidine treatment** reduced fasting insulin levels by 71% in SHROB and lowered plasma free fatty acids by 25%. In SHR, **moxonidine treatment** decreased free fatty acids by 17% compared with controls. During an oral glucose tolerance test, blood glucose levels in **moxonidine-treated** SHROB were reduced relative to untreated controls from 60 min onwards. Insulin secretion was facilitated at 30 min (83% greater) and 60 min (67% greater) postchallenge compared with control SHROB. In skeletal muscle, **moxonidine treatment** increased the expression of the insulin receptor beta subunit by 19% in SHROB but was without effect in SHR. The level of insulin receptor substrate-1 (IRS-1) protein was decreased by 60% in control SHROB compared with lean SHR. **Moxonidine treatment** enhanced the expression and insulin-stimulated phosphorylation of IRS-1 protein in skeletal muscle in SHROB by 74 and 27%, respectively, and in SHR by 40 and 56%, respectively. **Moxonidine** increased the levels of expression of IRS-1 protein in liver in SHR by 275% and in SHROB by 260%. These findings indicate that chronic inhibition of sympathetic activity with **moxonidine therapy** can lower free fatty acids and significantly improve insulin secretion, glucose disposal, and expression of key insulin signaling intermediates in an animal model of obese hypertension.

L73 ANSWER 69 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999197414 EMBASE A new type antihypertensive agent. Shan Z.-Z.; Dai S.-M.; Su D.-F.. Z.-Z. Shan, Dept of Pharmacology, Faculty to Basic Medicine, Second Military Medical University, Shanghai 200433, China. Chinese Pharmacological Bulletin 15/2 (102-105) 1999.
Refs: 20.
ISSN: 1001-1978. CODEN: ZYTOE8. Pub. Country: China. Language: Chinese.
Summary Language: English; Chinese.

AB **Moxonidine** is a second-generation, centrally acting antihypertensive drug with a distinctive mode of action. **Moxonidine** activates I1-imidazoline receptors (I1-receptors) in the rostroventrolateral medulla (RVLM), thereby reducing the activity of the **sympathetic nervous system**, leading to a pronounced and long-lasting blood pressure reduction. Chronic administration of **moxonidine** in hypertension effectively reduces the left ventricular hypertrophy and renal glomerulosclerosis. It is active against ventricular arrhythmia in a variety of experimental settings. It exerts beneficial effects on glucose metabolism and blood lipids in genetically hypertensive obese rats, and lowers intraocular pressure, suggesting a possible benefit in glaucoma. Side effects such as sedation or reduction in salive flow have been attributed only to actions at .alpha.2 adrenergic receptors of moxonidinc. Further studies are needed to verify the mechanism of this agent.

L73 ANSWER 70 OF 137 MEDLINE
1999417223 Document Number: 99417223. PubMed ID: 10489098.
**Moxonidine**: a new antiadrenergic antihypertensive agent. Prichard B N; Graham B R; Owens C W. (Centre of Clinical Pharmacology, University College London, UK. ) JOURNAL OF HYPERTENSION, (1999 Aug) 17 Suppl 3 S41-54. Ref: 69. Journal code: IEW; 8306882. ISSN: 0263-6352. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Moxonidine** is a centrally acting antihypertensive. Its action is mediated by imidazoline I1 receptors located in the rostral ventro-lateral medulla (RVLM). Animal experiments show that much smaller amounts are required to reduce blood pressure (BP) when it is given intracisternally, or injected directly into the RVLM, compared to intravenous dose.

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Pretreatment with imidazoline I1 blockade from efaroxan abolishes the antihypertensive action of microinjection of **moxonidine** into the RVLM in the spontaneously hypertensive rat (SHR), while alpha2 blockade from SKF 86466 is much less effective. Microinjection of efaroxan into the RVLM prevents the fall of BP in the SHR from intravenous **moxonidine**. **Moxonidine** binds with an affinity for the imidazoline I1 receptor that is 33 times more effective than is alpha2-receptor binding. There is only a few fold preference for binding at the imidazoline I1-receptor for clonidine. **Moxonidine** results in a fall in adrenaline, noradrenaline and renin levels in humans, as might be expected from central inhibition of sympathetic tone. **Moxonidine** gives a fall of BP due to a decline in systemic vascular resistance, while the heart rate, cardiac output, stroke volume and pulmonary artery pressures are not affected. There is a reduction in left-ventricular end systolic and diastolic volumes. There is a regression of left-ventricular hypertrophy after **moxonidine** was given for 6 months. Following oral administration the half-life (Tmax) is about 1 h. **Moxonidine** is highly bioavailable, approaching 90%. **Moxonidine** is largely excreted unchanged, biotransformation is unimportant. It has a T(1/2) of 2.5 h, renal insufficiency prolongs the T(1/2). However, suggesting possible retention in the central nervous system (CNS) the antihypertensive effect lasts longer than would be expected from the half-life. **Moxonidine** has been shown to be suitable for administration once daily. **Moxonidine** is an effective antihypertensive drug. In the course of its evaluation it has been compared with representatives from each important class of antihypertensive drugs, with diuretics, both alpha- and beta-blocking drugs, clonidine, calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors. These studies have shown that BP control is overall similar with **moxonidine** and these other agents. **Moxonidine** has a favourable side-effect profile, at least in part due to its lack of effect on central alpha2 receptors.

L73 ANSWER 71 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999337661 EMBASE [Evidence based medicine using **heart failure** as a paradigm]. EVIDENCE BASED MEDICINE AM BEISPIEL DER HERZINSUFFIZIENZ. Erdmann E.; Hanrath P.. Dr. E. Erdmann, Klinik III fur Innere Medizin, Universitat zu Koln, Joseph-Stelzmann-Strasse 9, 50924 Koln, Germany. Deutsche Medizinische Wochenschrift 124/SUPPL. 2 (S31) 24 Sep 1999.
ISSN: 0012-0472. CODEN: DMWOAX. Pub. Country: Germany. Language: German.

L73 ANSWER 72 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:471166 Document No.: PREV199900471166. **Moxonidine** improves insulin sensitivity in insulin-resistant hypertensives. Haenni, Arvo (1); Lithell, Hans. (1) Department of Public Health and Caring Sciences/Geriatrics, S-75125, Uppsala Sweden. Journal of Hypertension, (Aug., 1999) Vol. 17, No. SUPPL. 3, pp. S29-S35. ISSN: 0263-6352.
Language: English. Summary Language: English.
AB Objective: To study whether insulin sensitivity and insulin response are altered by **moxonidine treatment** in obese patients with mild essential hypertension. Design: a prospective, double-blind, placebo-controlled, randomized, parallel group study. Patients and methods: 77 patients with mild essential hypertension and body mass index > 27 were enrolled. A placebo run-in period of 1-3 weeks was followed by 8-9 weeks of double-blind **treatment** with either placebo or **moxonidine**. Patients receiving antihypertensive drugs underwent a 4-week wash-out period preceeding the placebo run-in. Insulin sensitivity was evaluated by hyperinsulinaemic euglycaemic clamp test. Insulin response was measured during intravenous glucose tolerance test. Results: 72 patients completed the study. No serious adverse events were reported. The glucose infusion rate (M value), and insulin sensitivity index (M/I

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ratio) increased in the **moxonidine-treated** subjects by 10% (P = 0.025), and 11% (P = 0.04), respectively,whereas the values in the placebo group remained unchanged. In the predefined insulin-resistant subgroup with M/I ratio < 3.6 at baseline, glucose infusion rate and insulin sensitivity index increased by 21% whereas values in the placebo group remained unchanged. A between-group comparison showed a statistical significant difference in the M value (P = 0.026) and a borderline statistical difference in the M/I ratio (P = 0.056) in favour of **moxonidine**. No statistically significant effects were seen in the subgroup with a M/I ratio gtoreq 3.6 at baseline. The insulin secretion in response to glucose stimulation was unaffected in insulin-resistant as well as in insulin-sensitive hypertensive patients. Conclusion: **moxonidine treatment** improved insulin sensitivity in insulin-resistant, obese patients with mild hypertension, but not in insulin-sensitive obese subjects with mild hypertension, when compared to placebo. Insulin response to glucose stimulation was unaffected. The drug was well tolerated.

L73 ANSWER 73 OF 137 MEDLINE DUPLICATE 19
1999180298 Document Number: 99180298. PubMed ID: 10082261. Facilitation of spontaneous defibrillation by **moxonidine** during regional ischaemia in an isolated working rabbit heart model. Wolk R; Kane K A; Cobbe S M; Hicks M N. (Department of Medical Cardiology, Royal Infirmary, Glasgow, UK. ) EUROPEAN JOURNAL OF PHARMACOLOGY, (1999 Feb 12) 367 (1) 25-32. Journal code: EN6; 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB **Moxonidine** has been shown to be antiarrhythmic during ischaemia in vivo. This study aimed to investigate its electrophysiological effects in isolated working rabbit hearts in vitro. Monophasic action potential duration, effective refractory period and conduction delay were measured at three ventricular sites. The hearts were **treated** before and during ischaemia and **reperfusion** with vehicle, **moxonidine** (0.01, 0.1 and 1 microM) or labetalol (1 microM). In all groups, ventricular fibrillation was always induced during ischaemia. Only 0.1 microM **moxonidine** decreased the incidence of sustained ventricular fibrillation from 86 to 17%, although it did not affect any electrophysiological parameters measured. Similarly, labetolol, an adrenoceptor blocker, facilitated spontaneous defibrillation without any electrophysiological effects. In conclusion, **moxonidine** directly facilitates spontaneous defibrillation of ventricular fibrillation during ischaemia. Since the same effect is observed with labetalol, it is possible that the defibrillatory action of **moxonidine** is related to its peripheral antiadrenergic activity, although other mechanisms cannot be excluded.

L73 ANSWER 74 OF 137 MEDLINE
1999417219 Document Number: 99417219. PubMed ID: 10489094. The renaissance of centrally acting antihypertensive drugs. van Zwieten P A. (Department of Pharmacotherapy, Academic Medical Centre, University of Amsterdam, The Netherlands. ) JOURNAL OF HYPERTENSION, (1999 Aug) 17 Suppl 3 S15-21. Ref: 49. Journal code: IEW; 8306882. ISSN: 0263-6352. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Classic centrally acting antihypertensive drugs such as clonidine, guanfacine and alpha-methyl-dioxyphenylalanine (alpha-methyl-DOPA) (via its active metabolite alpha-methyl-noradrenaline) are assumed to induce peripheral sympathoinhibition and a reduction in (elevated) blood pressure as a result of the stimulation of alpha2-adrenoceptors in the pons-medulla region in the brain. Their antihypertensive efficacy is beyond doubt, but their profile of adverse reactions is considered unfavourable when compared with most other antihypertensive drugs currently used, such as low-dose diuretics, beta-blockers, angiotensin-converting enzymes (ACE)-inhibitors, calcium antagonists, peripheral alpha1-adrenoceptor

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antagonists, and angiotensin II-receptor antagonists. More recently, central imidazoline (I1)-receptors have been recognized to be another target of centrally acting antihypertensive drugs. Clonidine is considered at present to be a mixed agonist that stimulates both alpha2- and I1-receptors. **Moxonidine** and rilmenidine are considered to be moderately selective I1-receptor stimulants, although it still remains unknown whether these agents act directly on the receptor as genuine agonists. The imidazoline (I1)-agonists also cause peripheral sympathoinhibition, triggered at the level of central nervous imidazoline receptors, predominantly in the rostral ventrolateral medulla. The imidazoline receptor stimulants are effective antihypertensives with a mode of action and haemodynamic profile which seems attractive from a pathophysiological point of view. **Moxonidine** and rilmenidine are considered preferable over the classic alpha2-adrenoceptor stimulants because of their pattern of side-effects, which may be explained on the basis of absent or weak affinity for the alpha2-adrenoceptor.

L73 ANSWER 75 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999319076 EMBASE [Old and new drugs for individual antihypertensive **therapy**]. NEUES UND BEWAHRTES FUR DIE INDIVIDUELLE **THERAPIE**. Stiefelhagen P.. MMW-Fortschritte der Medizin 141/34 (14-15) 26 Aug 1999.
ISSN: 1438-3276. CODEN: MFMEF8. Pub. Country: Germany. Language: German.

L73 ANSWER 76 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999051934 EMBASE [Change of paradigm in the **therapy** of **heart failure**]. PARADIGMENWECHSEL IN DER **THERAPIE**. Gilfrich H.-J.. Dr. H.-J. Gilfrich, Sankt Katharine-Krankenhaus, I. Medizinische Klinik, Seckbacher Landstrasse 65, 60 389 Frankfurt, Germany. Pharmazeutische Zeitung 144/3 (10-15) 21 Jan 1999.
Refs: 13.
ISSN: 0031-7136. CODEN: PZSED5. Pub. Country: Germany. Language: German.

L73 ANSWER 77 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999268536 EMBASE The role of neurohormonal antagonists in hibernating myocardium. Lahiri A.; Senior R.; Khattar R.. Dr. A. Lahiri, Department of Cardiology, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, United Kingdom. Journal of Cardiovascular Pharmacology 33/SUPPL. 3 (S9-S16) 1999.
Refs: 72.
ISSN: 0160-2446. CODEN: JCPCDT. Pub. Country: United States. Language: English. Summary Language: English.
AB Hibernating myocardium is characterized by chronic reduction of myocardial blood flow due to obstructive coronary artery disease, causing reversible left ventricular dysfunction and flow-metabolism mismatch. The condition is unstable and increasing demand may lead to further left ventricular dysfunction or necrosis causing death or worsening **heart failure**. Recognition of the condition is difficult and requires complex cardiac imaging protocols. **Treatment** protocols are also poorly defined. This review addresses both the diagnostic and **therapeutic** aspects of hibernating myocardium.

L73 ANSWER 78 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 20
1998:740045 Document No. 130:104651 Antihypertensive drugs interacting with central imidazoline (I1)-receptors. Van Zwieten, P. A. (Dep. Pharmacother., Cardiol. Cardiopulmonary Surg., Acad. Med. Cent., Univ. Amsterdam, Amsterdam, 1105 AZ, Neth.). Expert Opin. Invest. Drugs, 7(11), 1781-1793 (English) 1998. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications.
AB A review, with 66 refs. Central imidazoline (I1)-receptors have been recognized as targets of a new class of centrally acting

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antihypertensives. The stimulation of these I1-receptors induces peripheral sympatho-inhibition and a redn. of (elevated) blood pressure. **Moxonidine** and rilmenidine are the prototypes of this new class of centrally acting antihypertensives. These imidazoline receptor stimulants are effective antihypertensives with a hemodynamic profile which is attractive from a pathophysiol. point of view. Since both **moxonidine** and rilmenidine have a much weaker affinity for central .alpha.2-adrenoceptors than classic centrally acting drugs, for example, clonidine and .alpha.-methyl-DOPA, the side effects profile of the I1-receptor stimulants is significantly better. The imidazoline (I1)-receptor stimulants are the subject of the current survey. They appear to offer the possibility of developing centrally acting antihypertensives with the same attractive hemodynamic characteristics as the classic .alpha.2-adrenoceptor stimulants, but with clearly better tolerability. Their potential use in the **treatment** of congestive **heart failure** and the metabolic syndrome is subject to clin. investigation.

L73 ANSWER 79 OF 137 MEDLINE DUPLICATE 21
1999074212 Document Number: 99074212. PubMed ID: 9856967. I1-imidazoline agonist **moxonidine** decreases sympathetic nerve activity and blood pressure in hypertensives. Wenzel R R; Spieker L; Qui S; Shaw S; Luscher T F; Noll G. (Departments of Cardiology, Cardiovascular Research, and Clinical Research, University Hospital, Inselspital, Bern; (Switzerland). ) HYPERTENSION, (1998 Dec) 32 (6) 1022-7. Journal code: GK7; 7906255. ISSN: 0194-911X. Pub. country: United States. Language: English.

AB **Moxonidine** is an I1-imidazoline receptor agonist that reduces blood pressure in hypertensives. Experimental data suggest that **moxonidine** inhibits central sympathetic activity. However, whether such a mechanism is involved in vivo in humans is still unclear. We investigated the effects of 0.4 mg **moxonidine** orally on muscle sympathetic nerve activity and heart rate in an open study in 8 healthy volunteers. Furthermore, we studied the effects of 0.4 mg **moxonidine** on muscle sympathetic nerve activity, heart rate, blood pressure, 24-hour blood pressure profile, and hormone plasma levels in 25 untreated hypertensives in a double-blind, placebo-controlled study. **Moxonidine** decreased muscle sympathetic nerve activity in both healthy volunteers (P<0.05 versus baseline) and hypertensives (P<0.02 versus placebo). Plasma norepinephrine also decreased (P<0. 01), whereas plasma epinephrine and renin levels did not change (P=NS). Furthermore, **moxonidine** decreased systolic (P<0.0001) and diastolic (P<0.001) blood pressure. Heart rate decreased after **moxonidine** in healthy subjects (P<0.05); in hypertensives, heart rate decreased during the night hours (P<0.05) but not during daytime (P=NS). Plasma levels of LDL, HDL, and total cholesterol were not influenced by the drug (P=NS). **Moxonidine** decreases systolic and diastolic blood pressure by inhibiting central nervous sympathetic activity. This makes this new drug suitable for the **treatment** of human hypertension and possibly for other cardiovascular diseases with increased sympathetic nerve activity, ie, ischemic heart disease and **heart failure**
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L73 ANSWER 80 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998370295 EMBASE Antihypertensive to be evaluated in **heart failure**. British Journal of Cardiology 5/10 (509) 1998. ISSN: 0969-6113. CODEN: BJCAEM. Pub. Country: United Kingdom. Language: English.

L73 ANSWER 81 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 22
1998:582410 Document No. 129:325597 The potential clinical application of **moxonidine** in congestive **heart failure**. Motz,

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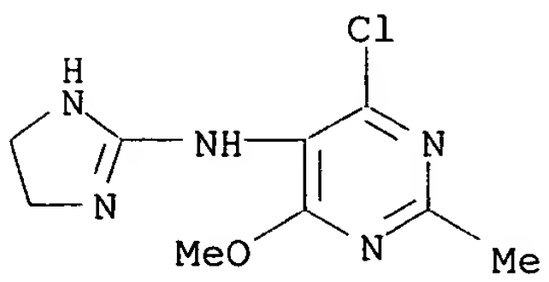
Wolfgang; Scheler, Sibylle; Mox, Bernhard (Karlsburg Cardiovascular Center, Karlsburg, D-17495, Germany). Rev. Contemp. Pharmacother., 9(7), 473-479 (English) 1998. CODEN: RCPHFW. ISSN: 0954-8602. Publisher: Marius Press.

AB A review with 39 refs. Sustained neuroendocrine activation plays a key role in chronic **heart failure**. Prognosis of **heart failure** is much worse the higher the plasma noradrenaline. In recent years, studies have shown the benefit of .beta.-receptor blockers on the clin. outcome of patients with congestive **heart failure**. Antisympathetic drugs may be an interesting alternative to peripheral .beta.- and .alpha.-receptor blockade. It is possible to diminish, or even antagonize, the effects mediated by .beta.- or .alpha.-receptors by central inhibition of the **sympathetic nervous system**. Cardiac .beta.-adrenoceptors are blocked more gradually, and the effects of noradrenaline, mediated by .alpha.-adrenoceptors in vessels and in the myocardium, are also blocked. Clonidine, which has been used as an antihypertensive drug for many years, suppresses the **sympathetic nervous system** by stimulating central .alpha.1-receptors, and reduces blood pressure as a result. **Treatment** of patients with congestive **heart failure** with clonidine leads to a redn. of myocardial contractility, while stroke vol. remains unchanged or is increased as a result of reduced systemic vascular resistance. **Moxonidine** is also an antisympathetic drug, but, unlike clonidine, its suppression of the **sympathetic nervous system** activity is mainly by stimulation of central imidazoline receptors, rather than by stimulation of the central .alpha.1-adrenoceptors. The adverse effects of **moxonidine** are less marked than those of clonidine. **Moxonidine** has been used in the management of chronic **heart failure** in a pilot study which showed it to be generally safe and well tolerated. The occurrence of transient, dose-related symptomatic hypotension in vulnerable patients can be managed by down-titrn. of the **moxonidine** dose. Whether initiation of **moxonidine therapy** is assocd. with fewer problems than **treatment** with .beta.-receptor blockers has to be detd. in future studies. It is concluded that the principle of antisympathetic **treatment** in congestive **heart failure** is worth reviving. Placebo-controlled studies in respect of long-term effects and mortality are needed.

IT **75438-57-2, Moxonidine**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**moxonidine** clin. potential in congestive **heart failure**)

RN 75438-57-2 CAPLUS

CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)




L73 ANSWER 82 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998216190 EMBASE Autonomic nervous system as a target for cardiovascular

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drugs. Bousquet P.; Monassier L.; Feldman J.. Prof. P. Bousquet, Lab Neurobiol./Pharmacol. Cardiovasc, Universite Louis Pasteur, CNRS, 11 rue Humann, 67000 Strasbourg, France. Pascal.Bousquet@medecine.u-strasbg.fr. Clinical and Experimental Pharmacology and Physiology 25/6 (446-448) 1998.
Refs: 27.
ISSN: 0305-1870. CODEN: CEXPB. Pub. Country: Australia. Language: English. Summary Language: English.

AB 1. Drugs acting within the autonomic nervous system (ANS) are of particular interest when autonomic abnormalities are implicated in the development and maintenance of various cardiovascular pathologies. For examples, it has been documented that in the early stages of hypertensive disease (i.e. hyperkinetic borderline hypertension) a sympathetic hyperactivity associated with a decreased parasympathetic activity results in increased cardiac output and heart rate. 2. Several classes of drugs acting within the central, as well as the peripheral ANS, are very efficient in **treating** hypertensive disease. One of these classes of drugs, the second generation of centrally acting drugs, has proved beneficial in this respect because, in addition to their **therapeutic** efficacy, these drugs are well tolerated. 3. The central nervous system may also be the target for drugs with the potential to **treat** other cardiovascular diseases. Some recent experimental and clinical data supporting such new perspectives concerning idiopathic dysrhythmias, angina pectoris and congestive **heart failure** will be summarized.

L73 ANSWER 83 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998301574 EMBASE The I1-imidazoline receptor agonist **moxonidine**: Molecular, cellular and organismic actions. Ernsberger P.. P. Ernsberger, Dept of Medicine (Hypertension), Case Western Univ School of Medicine, Cleveland, OH 44106-4982, United States. Reviews in Contemporary Pharmacotherapy 9/7 (441-462) 1998.
Refs: 226.
ISSN: 0954-8602. CODEN: RCPHFW. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB **Moxonidine** is a centrally-acting antihypertensive with a unique structure consisting of two heterocyclic rings, which acts selectively on lower brainstem centres to reduce sympathetic nervous activity without major interference with higher brain functioning. **Moxonidine** achieves this targeted action by stimulating a novel neurotransmitter receptor found mainly in the brainstem, adrenal medulla and kidney. The I1-imidazoline receptor activated by **moxonidine** works through arachidonic acid and phospholipid signalling cascades in neuronal cells, with the net result of inhibiting sympathetic premotor neurones. **Moxonidine** also activates .alpha.2-adrenergic receptors, although to a lesser extent than clonidine, which results in some residual adverse effects such as dry mouth and sedation. In addition to its antihypertensive action, **moxonidine** may also promote sodium excretion, improve insulin resistance and glucose tolerance, reduce gastric acid production, and protect against hypertensive target organ damage such as kidney disease and **cardiac hypertrophy**.

L73 ANSWER 84 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 23
1998:582407 Document No. 129:342108 The rationale for sympathetic modulation in NIDDM and the insulin resistance syndrome. Rosen, Peter; Rosen, Renate (Diabetes Research Institute, Heinrich-Heine-Universitat, Dusseldorf, D-40225, Germany). Rev. Contemp. Pharmacother., 9(7), 429-439 (English) 1998. CODEN: RCPHFW. ISSN: 0954-8602. Publisher: Marius Press.

AB A review, with 94 refs. In recent years it has become clear that insulin resistance is both a typical characteristic of non-insulin-dependent (type 2) diabetes (NIDDM) and a common feature, and presumably the pathophysiol. cause, of the "metabolic syndrome" ("insulin resistance syndrome" or

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"syndrome X") which describes the close assocn. between various cardiovascular risk factors, such as obesity, hypertension and dyslipidemia. This hypothesis is supported by the detection of insulin resistance in many young hypertensive patients and normotensive offspring of hypertensive parents, and by a frequent assocn. between an increase in insulin sensitivity and a redn. in blood pressure. The identification of insulin resistant patients, and the improvement of insulin sensitivity, should therefore be major goals in the effort to reduce cardiovascular morbidity and mortality in western societies. While the pathophysiol. of insulin resistance is not yet fully understood, there is evidence that besides various defects in the target cells of insulin (primarily skeletal muscle, adipose tissue and the liver), central mechanisms leading to an activation of the hypothalamic-pituitary-adrenal axis and of sympathetic nerves play a major role. **Moxonidine**, a centrally acting antihypertensive compd., inhibits the **sympathetic nervous system**, and has therefore been proposed as having **therapeutic** value in **treating** both hypertension and insulin resistance. This view is supported by studies using various exptl. animal models, in all of which **moxonidine** led to significant improvement in insulin sensitivity accompanied by a redn. in elevated triglycerides and body wt. In hypertensive animals, blood pressure and proteinuria were also reduced. Though early clin. data are too few for final conclusions to be drawn, they are nevertheless in line with the exptl. findings. There is thus strong evidence that modulation of **sympathetic nervous system** activity by centrally acting compds. represents an interesting new approach to the **treatment** of insulin-resistance patients.

L73 ANSWER 85 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

1998301572 EMBASE Contribution of **sympathetic nervous system** overactivity to cardiovascular and metabolic disease.

Ernsberger P.; Koletsky R.J.; Friedman J.E.. P. Ernsberger, Departments of Medicine, Case Western Univ School of Medicine, Cleveland, OH 44106-4982, United States. Reviews in Contemporary Pharmacotherapy 9/7 (411-428) 1998.

Refs: 193.

ISSN: 0954-8602. CODEN: RCPHFW. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The **sympathetic nervous system** regulates cardiovascular and metabolic processes that maintain homoeostasis and mediate adaptations to environmental changes. Control of the sympathetic system is initiated through afferent signals to the brain, and then processed by the limbic system and hypothalamus. Integration of signals from throughout the brain occurs in the rostral ventrolateral medulla (RVLM) region. The RVLM then transmits signals through the spinal cord to sympathetic nerve terminals and the adrenal medulla. The resultant catecholamine stimulation evokes a generalized fight-or-flight response that activates metabolic pathways and cardiovascular adaptations to maintain energy supplies to organs and tissues. The **sympathetic nervous system** may play a role in pathophysiological responses to salt balance and weight cycling. The consequences of sympathetic overactivity include: adverse changes in the cardiovascular system leading to the development and maintenance of hypertension; target organ damage; **cardiac hypertrophy; heart failure** and arrhythmias; and constriction to blood vessels leading to damage to the heart, kidney and brain. Metabolic consequences of catecholamine excess include hyperglycaemia and hyperlipidaemia. Combined cardiovascular and metabolic abnormalities, resembling human metabolic syndrome X, which are produced by sympathetic overstimulation, promote coronary heart disease and stroke. Drugs that attenuate sympathetic activity hold particular promise in reducing the multiple abnormalities that occur with chronic overstimulation of the sympathoadrenal system.

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L73 ANSWER 86 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998394423 EMBASE [**Therapy** concepts in chronic congestive **heart failure** using new substances].
**THERAPIEKONZEPTE** DER HERZINSUFFIZIENZ MIT NEUEN SUBSTANZEN.
Thormann J.; Mitrovic V.; Bahavar H.. Dr. J. Thormann, Kerckhoff-Klinik (Kardiologie), Max-Planck-Gesellschaft Physiolog., Klinische Forschung, Beneke-Str. 2-8, 61231 Bad Nauheim, Germany. Herz Kreislauf 30/11 (382-393) 1998.
Refs: 77.
ISSN: 0046-7324. CODEN: HZKLAV. Pub. Country: Germany. Language: German.
Summary Language: English; German.

AB 20 years of ACE inhibitor drugs clearly have revolutionized **therapy** of cardiac failure, however neither quality of life nor life expectancy have improved substantially. Pathophysiologic considerations are indeed the basis for effective **therapy** of cardiac failure.. New **therapeutic** dispositions must be tested by prospective studies and consider prolongation of life as well. Never since the initiation of ACE inhibitor **therapy** has there been a new drug standing the test of time as a superior **therapeutic** scheme, except, perhaps, for .beta.-blocking agents. The primary most effective **therapeutic** strategy in cardiac failure today is arterial and venous vasodilation, mediated by the inhibition of neuro-endocrine vasoconstrictors. Presented are the following new **therapeutic** concepts: 1. Endotheline-Antagonism: The principle of action, the pharmacologic inhibition of endotheline activities, is mediated directly via endotheline-receptor-antagonism, or via inhibition of endotheline-converting-enzyme, or indirectly via angiotensin II-inhibition. Endotheline antagonism induces a peripheral vessel dilatation in cardiac failure, which in turn leads to an increase of heart rate and stroke index; this also works during classic **therapy** for cardiac failure and ACE-inhibitors being withdrawn. Endotheline-antagonism with an optimal hemodynamic efficacy has not been approved yet. 2. Moxonidin, an imidazolin receptor agonist with its centrally mediated sympatholytic effects is used as an antihypertensive agent (quite similar to clonidin but without its side effects). 3. Tedisamil, a K+-channel blocking agent with bradycardiac effects, inducing MVO2- reduction twofold: by slowing the heart rate and by prolonging diastolic coronary flow duration, which in turn has antiischemic effects without loss of inotropy. 4. Levosimendan, a Ca2+-sensitizer produces both positive inotropic and vasodilatory effects ('inodilator'). Its antiischemic property (propagated in a manner quite like in phosphodiesterase-III-inhibition) is thought to be due to vasodilation, whereby MVO2 is reduced; all in all very useful for the **therapy** of chronic **heart failure**;
prognostic advantages have yet to be shown, however.

L73 ANSWER 87 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998331688 EMBASE **Heart Failure**, 23 April 1998, Chester, UK. McGrath J.C.; McMurray J.; Dargie H.J.; McKenna W.J.; Poole-Wilson P.. British Journal of Clinical Pharmacology 46/4 (360-362) 1998.
ISSN: 0306-5251. CODEN: BCPHBM. Pub. Country: United Kingdom. Language: English.

L73 ANSWER 88 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998237275 EMBASE Recent developments with antihypertensive drugs: Focus on **moxonidine**. Elliott H.L.. Dr. H.L. Elliott, Dept. of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, United Kingdom. British Journal of Cardiology 5/6 (337-341) 1998.
Refs: 19.
ISSN: 0969-6113. CODEN: BJCAEM. Pub. Country: United Kingdom. Language: English.

Searched by: Mary Hale 308-4258 CM-1 12D16

L73 ANSWER 89 OF 137 MEDLINE DUPLICATE 24
1999066896 Document Number: 99066896. PubMed ID: 9851571. Increased **sympathetic nervous system** activity and its **therapeutic** reduction in arterial hypertension, portal hypertension and **heart failure**. Esler M; Kaye D. (Baker Medical Research Institute, Prahran, Melbourne, Australia.. esler@baker.edu.au) . JOURNAL OF THE AUTONOMIC NERVOUS SYSTEM, (1998 Oct 15) 72 (2-3) 210-9. Ref: 47. Journal code: H97; 8003419. ISSN: 0165-1838. Pub. country: Netherlands. Language: English.

AB Although the underlying mechanisms no doubt differ, activation of the **sympathetic nervous system** is an important pathophysiological feature in primary arterial hypertension, in portal hypertension accompanying hepatic cirrhosis, and in **heart failure**, and is a logical **therapeutic** target for centrally acting **sympathetic nervous system** suppressant drugs. Portal hypertension: The sympathetic outflows to skeletal muscle vasculature, the heart, the kidneys and to the hepatomesenteric circulation are stimulated in patients with alcoholic cirrhosis of the liver, perhaps as a reflex response to the vasodilatation and vascular shunting present. Acute dosing with clonidine produces dose dependent reduction in noradrenaline spillover from visceral organs and reduction in hepatic vein wedge pressure, with preservation of hepatic blood flow and negligible fall in arterial pressure. These findings indicate the clinical potential of drugs such as clonidine, **moxonidine** and rilmenidine for chronically lowering portal venous pressure in cirrhosis. Arterial hypertension: Activation of the sympathetic outflow to the heart, kidneys and skeletal muscle vasculature is commonly present in younger (< 45 years) patients with essential hypertension. The sympathetic stimulation appears to have adverse consequences in hypertensive patients beyond blood pressure elevation. Neural vasoconstriction in skeletal muscle has metabolic effects by impairing glucose delivery, which is a basis for insulin resistance and hyperinsulinemia. Within the heart a trophic effect of sympathetic activation on cardiac growth, contributing to the development of left ventricular hypertrophy, and an arrhythmogenic effect are also likely. Cardiac failure: The cardiac sympathetic nerves are preferentially stimulated in severe **heart failure**, with norepinephrine release from the failing heart at rest being increased as much as 50-fold, similar to the level seen in healthy people during near maximum exercise. This preferential activation of the cardiac sympathetic outflow contributes to arrhythmogenesis and possibly to progression of the **heart failure**, and has been directly linked to mortality; a high rate of spillover of noradrenaline from the heart is a strong, independent predictor of poor prognosis in severe cardiac failure. The mechanisms underlying sympathetic nervous stimulation are not entirely clear. Increased intracardiac diastolic pressure seems to be one peripheral signal, and increased forebrain norepinephrine turnover an important central mechanism. Following the demonstration of the beneficial effect of the beta-adrenergic blocker, carvedilol, and with second generation centrally acting sympathetic suppressants now under clinical investigation, elucidation of the abnormalities in central nervous control of sympathetic outflow in **heart failure** has become clinically relevant.

L73 ANSWER 90 OF 137 MEDLINE DUPLICATE 25
1999011974 Document Number: 99011974. PubMed ID: 9795882. Assumption testing in population pharmacokinetic models: illustrated with an analysis of **moxonidine** data from congestive **heart failure** patients. Karlsson M O; Jonsson E N; Wiltse C G; Wade J R. (Department of Pharmacy, Uppsala University, Sweden. ) JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS, (1998 Apr) 26 (2) 207-46. Journal code: JOV; 0357115. ISSN: 0090-466X. Pub. country: United States.

Searched by: Mary Hale 308-4258 CM-1 12D16

Language: English.

AB Deriving a population pharmacokinetic model from real data is always associated with numerous assumptions. Violations of these assumptions, especially if undetected, may lead to inappropriate conclusions being made from the analysis. Routinely, only a few of the assumptions are explicitly stated and justified in the reporting of a population model. Here, we attempt to be exhaustive in the presentation of the assumptions made in the course of an analysis of **moxonidine** pharmacokinetics. The different ways that assumptions were justified, through experience, graphical examination, or additional modeling, are outlined. Models for relaxing assumptions regarding the covariate and statistical submodels, not previously reported in the area of population pharmacokinetic modeling, are also described.

L73 ANSWER 91 OF 137 MEDLINE DUPLICATE 26

1999066894 Document Number: 99066894. PubMed ID: 9851569. Comparison of the baroreceptor-heart rate reflex effects of **moxonidine**, rilmenidine and clonidine in conscious rabbits. Godwin S J; Tortelli C F; Parkin M L; Head G A. (Neuropharmacology Laboratory, Baker Medical Research Institute, Melbourne, Victoria, Australia. ) JOURNAL OF THE AUTONOMIC NERVOUS SYSTEM, (1998 Oct 15) 72 (2-3) 195-204. Journal code: H97; 8003419. ISSN: 0165-1838. Pub. country: Netherlands. Language: English.

AB In 10 conscious rabbits, the baroreceptor-heart rate (HR) reflex effects of centrally acting antihypertensive agents with high affinity for imidazoline receptors (IRs), **moxonidine** and rilmenidine, were compared with clonidine which acts predominantly via central alpha2-adrenoceptors. Dose regimens were chosen to give similar hypotension (-17+/-1 mm Hg) and bradycardia (-27+/-2 b/min) for all three agents given into the fourth ventricle. Baroreceptor-HR reflex curves were assessed by i.v. drug induced changes in blood pressure. With all **treatments**, the baroreflex curves with both vagal and sympathetic effectors intact were shifted to the left, corresponding to the hypotension, and the bradycardia plateau was reduced. Rilmenidine and **moxonidine** also reduced the upper plateau such that the curves were shifted parallel down the HR scale with no change in the HR range. By contrast, clonidine only decreased the lower plateau, and thus increased HR range (+19+/-6%). **Moxonidine**, but not rilmenidine, reduced the baroreflex gain by reducing the curvature. Clonidine also decreased curvature but this did not result in a reduction in gain as it was offset by the increase in HR range. The gain and range of the cardiac sympathetic component, as assessed after vagal blockade, was reduced by rilmenidine by 53 and 40% respectively, but was not affected by the other agents. The calculated vagal component of the curves showed that all agents produced a greater vagal bradycardia in response to a rise in pressure and that both rilmenidine and clonidine increased vagal HR range. The present study results show that many of the baroreflex effects of clonidine, such as facilitating cardiac vagal responses, are shared by the second generation agent rilmenidine, suggesting that they are primarily due to alpha2-adrenoceptor activation. In addition, the inhibition of the sympathetic component of the baroreflex, observed with rilmenidine, and not clonidine suggests that this effect may involve IRs. By contrast **moxonidine**, the most specific agent for I1 receptors, produces mainly a baroreflex independent inhibition of cardiac sympathetic activity with little effect on vagal activity.

L73 ANSWER 92 OF 137 MEDLINE

1998349066 Document Number: 98349066. PubMed ID: 9684437. Centrally acting antihypertensives: not obsolete after all. Schachter M. (Department of Clinical Pharmacology, Imperial College School of Medicine, St Mary's Hospital, London, UK. ) INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, (1998 Apr-May) 52 (3) 192-5. Journal code: CVT; 9712381. ISSN: 1368-5031. Pub.

Searched by: Mary Hale 308-4258 CM-1 12D16

country: ENGLAND: United Kingdom. Language: English.

AB Centrally acting antihypertensive drugs, or sympatholytics, have a long history of efficacy, including some of the earliest major clinical trials, but they are now little used in the UK and elsewhere. This has been due to the introduction of new drugs with better tolerability than the centrally acting agents. In the case of clonidine there was also concern about rebound hypertension. However, at least some hypertensives may benefit from a centrally acting drug and a new class of agents, the imidazoline agonists, has recently been developed. One of these, **moxonidine**, is available in the UK. Clinical studies so far suggest that its efficacy is comparable to currently used drugs and that adverse effects are less severe than with earlier sympatholytics. Rebound hypertension has not been described, so this may lead to a revival in interest in these drugs as antihypertensive agents.

L73 ANSWER 93 OF 137 MEDLINE

1998111516 Document Number: 98111516. PubMed ID: 9449863. Selective imidazoline receptor agonists for metabolic syndrome. Krentz A J; Evans A J. (Department of Diabetes and Endocrinology, Southampton General Hospital, UK. ) LANCET, (1998 Jan 17) 351 (9097) 152-3. Journal code: L0S; 2985213R. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

L73 ANSWER 94 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 27

1998:292115 Document No. 129:49042 Imidazoline receptor ligands: cardiovascular applications. Bousquet, P.; Feldman, J.; Monassier, L. (Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, ULP - CNRS, Strasbourg, 67085, Fr.). Emerging Drugs, 3, 113-120 (English) 1998. CODEN: EMDRFV. ISSN: 1361-9195. Publisher: Ashley Publications.

AB Hypertension, congestive **heart failure** and cardiac arrhythmias are very common cardiovascular diseases; e.g., the prevalence of hypertension was estd. as .apprx.10% of the adult population of industrial countries. The discovery and development of new antihypertensive drugs is justified by the fact that most of the available drugs act predominantly to reduce blood pressure alone and have only minimal effects on the risk factors assocd. with hypertension. The angiotensin converting enzyme (ACE) inhibitors were the 1st antihypertensive drugs to exhibit addnl. beneficial effects, such as a redn. in **cardiac hypertrophy**. Ligands selective for cerebral imidazoline-specific receptors are known to inhibit sympathetic activity and to restore sympatho-vagal balance. Rilmenidine and, more recently, **moxonidine** (representatives of the so-called 2nd generation of centrally-acting cardiovascular drugs) were the 1st centrally-acting, imidazoline receptor-specific antihypertensive agents to be marketed as cardiovascular drugs. They may also be of benefit in the **treatment** of Syndrome X, through a combination of their antihypertensive and sympatho-inhibitory actions. Because the sympatho-vagal balance is also altered in congestive **heart failure**, imidazoline-like drugs are also expected to be of benefit in this prevalent disease. Imidazoline-like drugs have already been shown to prevent the occurrence of cardiac arrhythmias in animal models; such an anti-arrhythmic action occurring at doses below that necessary to exert an antihypertensive effect. Therefore, imidazoline-like drugs may also be of benefit as anti-arrhythmic drugs. The available imidazoline-like drugs are well tolerated. Existing **therapies** for cardiac arrhythmias and congestive **heart failure** suffer from deleterious side-effect profiles and/or minimal efficacy. Therefore, it is hoped that imidazoline-like drugs will lead to well-tolerated, efficacious drugs for the **treatment** of not only hypertension but also some of the risk factors assocd. with hypertension, in addn. to cardiac arrhythmias and congestive **heart failure**. Whether the efficacy of such compds. in man will be more favorable than that of currently

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available **therapies** remains to be detd. A review with 29 refs.

L73 ANSWER 95 OF 137 MEDLINE DUPLICATE 28
1999066882 Document Number: 99066882. PubMed ID: 9851557. Does a second generation of centrally acting antihypertensive drugs really exist?. Feldman J; Greney H; Monassier L; Vonthron C; Bruban V; Dontenwill M; Bousquet P. (Laboratoire de Neurobiologie et Pharmacologie Cardiovasculaire, Faculte de Medecine, CNRS-Universite Louis Pasteur, Strasbourg, France. ) JOURNAL OF THE AUTONOMIC NERVOUS SYSTEM, (1998 Oct 15) 72 (2-3) 94-7. Ref: 42. Journal code: H97; 8003419. ISSN: 0165-1838. Pub. country: Netherlands. Language: English.

AB The site of the hypotensive action of imidazoline compounds, such as clonidine, was first identified within the rostroventrolateral part of the brainstem: the nucleus reticularis lateralis. After that, it was shown that imidazolines and related substances reduced blood pressure when applied in this area whereas catecholamines were not capable of producing such an effect. These data led us to suggest the existence of receptors specific for imidazoline-like compounds different from the alpha2-adrenoceptors. Soon after, the existence of imidazoline binding sites was reported in the brain and in a variety of peripheral tissues including the human kidney. As expected, these specific binding sites do not bind the catecholamines. The imidazoline binding sites are already subclassified in two groups: the I1-subtype sensitive to clonidine and idazoxan, and the I2-subtype, sensitive to idazoxan and nearly insensitive to clonidine. Functional studies confirmed that the hypotensive effects of clonidine-like drugs involved imidazoline receptors while their most frequent side effects only involved alpha2-adrenoceptors. However, recent functional evidence suggests that a cross talk between imidazoline receptors and alpha2-adrenoceptors is necessary to trigger a hypotensive effect within the ventral brainstem. Rilmenidine and **Moxonidine** are the leader compounds of a new class of antihypertensive drugs selective for imidazoline receptors. At hypotensive doses, these drugs are devoid of significant sedative effect. Rilmenidine evoked hypotension when injected within the nucleus reticularis lateralis region; it competed for [3H]-clonidine bound to specific imidazoline binding sites in human medullary membrane preparations but proved more selective for cerebral imidazoline receptors than clonidine. It is suggested that this selectivity might explain the low incidence of their side effects. Additional potentially beneficial actions on cardiac arrhythmias or congestive **heart failure** enlarge the **therapeutic** interest of imidazoline-related drugs. Recent binding and functional data throw a new light on the optimal pharmacological profile of this second generation of centrally acting antihypertensive drugs.

L73 ANSWER 96 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998327095 EMBASE [**Moxonidine**: Antisympathotonic **therapy** influences insulin resistance]. ANTISYMPATHOTONE **THERAPIE** BEEINFLUSST INSULINRESISTENZ. Fortschritte der Medizin 116/27 (51-52) 30 Sep 1998.
ISSN: 0015-8178. CODEN: FMDZAR. Pub. Country: Germany. Language: German.

L73 ANSWER 97 OF 137 MEDLINE DUPLICATE 29
1999253370 Document Number: 99253370. PubMed ID: 10321453. Anti-hyperglycemic activity of **moxonidine**: metabolic and molecular effects in obese spontaneously hypertensive rats. Friedman J E; Ishizuka T; Liu S; Farrell C J; Koletsky R J; Bedol D; Ernsberger P. (Department of Nutrition, Case Western Reserve University School of Medicine, Cleveland, OH 44106-4935, USA.. jef8@po.cwru.edu) . BLOOD PRESSURE, (1998) Suppl 3 32-9. Journal code: BYA; 9301454. ISSN: 0803-7051. Pub. country: Norway. Language: English.

AB Hypertension and insulin resistance are often part of a complex set of

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abnormalities including obesity, hyperlipidemia, and glucose intolerance, described as syndrome X. Besides a common genetic basis, insulin resistance and hypertension might be linked by excessive activity of the **sympathetic nervous system**. We studied the effects of chronic inhibition of sympathetic activity with the antihypertensive agent **moxonidine** on glucose metabolism in the genetically obese SHR Koletsky rat (SHROB), a unique animal model which closely resembles human syndrome X, expressing genetic obesity, hypertension, and hyperlipidemia. **Moxonidine**, a selective I1-imidazoline receptor agonist, was administered to SHROB and SHR for 90 days in food at 8 mg/kg/day. **Moxonidine** not only lowered blood pressure, but also reduced fasting insulin levels by 49% in SHROB, and reduced plasma free fatty acids by 30%. In lean SHR, **moxonidine treatment** decreased circulating free fatty acids by 33% compared to controls. During oral glucose tolerance tests, blood glucose levels in **moxonidine-treated** SHROB were reduced from 60 min onwards, and there was a sharply higher insulin secretion post-challenge compared to control SHROB. Western blot analysis of insulin signaling proteins showed that IRS-1 was decreased 42% in control SHROB compared with SHR. **Moxonidine treatment** enhanced the expression of IRS-1 protein in skeletal muscle by 74% in SHROB and 40% in SHR. **Moxonidine** increased expression of IRS-1 protein in liver by 245% in SHROB and 268% in SHR. Long-term inhibition of sympathetic activity with **moxonidine therapy** lowered free fatty acids and significantly improved insulin secretion, glucose disposal, and expression of key insulin signaling intermediates. Thus, **moxonidine** should be considered for the **treatment** of multiple metabolic and cardiovascular abnormalities associated with syndrome X.

L73 ANSWER 98 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 30

1999:244765 Document No.: PREV199900244765. Anti-hyperglycemic activity of **moxonidine**: Metabolic and molecular effects in obese spontaneously hypertensive rats. Friedman, Jacob E. (1); Ishizuka, Tatsuya; Liu, Sha; Farrell, Craig J.; Koletsky, Richard J.; Bedol, David; Ernsberger, Paul. (1) Department of Nutrition, School of Medicine, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH, 44106-4935 USA. Blood Pressure, (1998) Vol. 7, No. SUPPL. 3, pp. 32-39. ISSN: 0803-7051. Language: English. Summary Language: English.

AB Hypertension and insulin resistance are often part of a complex set of abnormalities including obesity, hyperlipidemia, and glucose intolerance, described as syndrome X. Besides a common genetic basis, insulin resistance and hypertension might be linked by excessive activity of the **sympathetic nervous system**. We studied the effects of chronic inhibition of sympathetic activity with the antihypertensive agent **moxonidine** on glucose metabolism in the genetically obese SHR Koletsky rat (SHROB), a unique animal model which closely resembles human syndrome X, expressing genetic obesity, hypertension, and hyperlipidemia. **Moxonidine**, a selective I1-imidazoline receptor agonist, was administered to SHROB and SHR for 90 days in food at 8 mg/kg/day. **Moxonidine** not only lowered blood pressure, but also reduced fasting insulin levels by 49% in SHROB, and reduced plasma free fatty acids by 30%. In lean SHR, **moxonidine treatment** decreased circulating free fatty acids by 33% compared to controls. During oral glucose tolerance tests, blood glucose levels in **moxonidine-treated** SHROB were reduced from 60 min onwards, and there was a sharply higher insulin secretion post-challenge compared to control SHROB. Western blot analysis of insulin signaling proteins showed that IRS-1 was decreased 42% in control SHROB compared with SHR. **Moxonidine treatment** enhanced the expression of IRS-1 protein in skeletal muscle by 74% in SHROB and 40% in SHR. **Moxonidine** increased expression of IRS-1 protein in liver by 245%

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in SHROB and 268% in SHR. Long-term inhibition of sympathetic activity with **moxonidine therapy** lowered free fatty acids and significantly improved insulin secretion, glucose disposal, and expression of key insulin signaling intermediates. Thus, **moxonidine** should be considered for the **treatment** of multiple metabolic and cardiovascular abnormalities associated with syndrome X.

L73 ANSWER 99 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998318284 EMBASE High blood pressure management: Potential benefits of I1 agents. Esler M.. Prof. M. Esler, Baker Medical Research Institute, PO Box 6492, Melbourne 8008, Australia. Journal of Hypertension, Supplement 16/3 (S19-S24) 1998.
Refs: 47.
ISSN: 0952-1178. CODEN: JHSUEW. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB **Sympathetic nervous system** and hypertension. Biochemical, electrophysiological, pharmacological and haemodynamic findings support the existence of **sympathetic nervous system** activation in primary human hypertension. Analysis of regional **sympathetic nervous system** function, using both neurophysiological methods for measuring sympathetic nerve firing rates, and neurochemical techniques for quantifying regional noradrenaline spillover to plasma has demonstrated activation of the sympathetic nervous outflows to the heart, the kidneys, and skeletal muscle vasculature, particularly in younger patients. The initiating cause of this sympathetic nervous stimulation is unknown, but estimation of central nervous system noradrenaline turnover in hypertensive patients, using measurements of the washout of noradrenaline and its lipophilic metabolites into the internal jugular veins, indicates that activation of forebrain pressor noradrenergic nuclei is the probable underlying mechanism. Consequences of increased sympathetic activity. The sympathetic activation present in human hypertension no doubt contributes to the blood pressure elevation, and is a legitimate target for **therapeutic** intervention with imidazoline receptor-binding agents such as rilmenidine. In addition, the sympathetic nervous activation seems to have adverse consequences in hypertensive patients beyond initiating the blood pressure elevation. There is evidence that neural vasoconstriction has metabolic effects, in skeletal muscle impairing glucose delivery to muscle, causing insulin resistance and hyperinsulinaemia, and in liver retarding postprandial clearing of lipids, contributing to hyperlipidaemia. Cardiac sympathetic activation is demonstrably a cause of sudden death in **heart failure** patients; a comparable arrhythmogenic effect is probable in hypertension. A trophic effect of sympathetic activation on cardiovascular growth is also likely, contributing to the development of left ventricular hypertrophy. Rilmenidine, through its central nervous system actions, has been demonstrated to powerfully reduce sympathetic nervous activity in essential hypertension patients. Inhibiting the sympathetic system. As the clinical consequences of sympathetic nervous activation in essential hypertension appear to go beyond that of hypertension pathogenesis, extending to a causal influence in atherosclerosis development, **cardiovascular hypertrophy** and cardiac arrhythmias, it is possible that, of all antihypertensive drugs, those inhibiting the **sympathetic nervous system** might best reduce cardiovascular risk. This remains to be tested.

L73 ANSWER 100 OF 137 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 31
1999:237807 Document No.: PREV199900237807. The **sympathetic nervous system** and the kidney: Its importance in renal diseases. Ritz, Eberhard (1); Amann, Kerstin; Fliser, Danilo. (1) Department Internal Medicine, University of Heidelberg, Bergheimer Strasse

Searched by: Mary Hale 308-4258 CM-1 12D16

56 a, DE-69115, Heidelberg Germany. Blood Pressure, (1998) Vol. 7, No. SUPPL. 3, pp. 14-19. ISSN: 0803-7051. Language: English. Summary Language: English.

AB There is a two-way relation between the sympathetic nerve system and the kidney. On the one hand the sympathetic nerve system affects renal function, i.e. renal hemodynamics, renin secretion and tubular sodium transport. On the other hand the kidney is the source of activating afferent signals, presumably via stimulation of chemoreceptors and baroreceptors. This concept is supported by clinical observations in endstage and pre-endstage renal disease, where sympathetic overactivity is present. It has been shown to depend on the presence of the diseased kidney and is abolished by bilateral nephrectomy. Experimentally, interruption of afferent nerve traffic by dorsal rhizotomy partially prevents hypertension in renal damage models. Imidazoline-preferring binding sites are found in the kidney. In the rat, natriuresis is elicited by injection of **moxonidine** into the renal artery. In humans, there is no definite evidence for a natriuretic effect, but some observations point in this direction. In renal disease, the issue arises whether sympathetic overactivity contributes to progression of renal failure. Indirect evidence in this direction could be the marked acceleration of progression by smoking, a state of known sympathetic overactivity. In experimental models of renal damage, **treatment** with **moxonidine** in antihypertensive doses markedly attenuated development of glomerulosclerosis. Preliminary observations show that even non-antihypertensive doses of **moxonidine** interfere with the development of glomerulosclerosis. Sympathicolytic agents are obviously rational in the antihypertensive **therapy** of the renal patient, because uraemia is a state of sympathetic overactivity and because blood pressure-independent effects of sympathetic activation on progression are likely.

L73 ANSWER 101 OF 137 MEDLINE

1999253366 Document Number: 99253366. PubMed ID: 10321449. The **sympathetic nervous system** and the kidney: its importance in renal diseases. Ritz E; Amann K; Fliser D. (Department of Internal Medicine, University of Heidelberg, Germany. ) BLOOD PRESSURE, (1998) Suppl 3 14-9. Ref: 35. Journal code: BYA; 9301454. ISSN: 0803-7051. Pub. country: Norway. Language: English.

AB There is a two-way relation between the sympathetic nerve system and the kidney. On the one hand the sympathetic nerve system affects renal function, i.e. renal hemodynamics, renin secretion and tubular sodium transport. On the other hand the kidney is the source of activating afferent signals, presumably via stimulation of chemoreceptors and baroreceptors. This concept is supported by clinical observations in endstage and pre-endstage renal disease, where sympathetic overactivity is present. It has been shown to depend on the presence of the diseased kidney and is abolished by bilateral nephrectomy. Experimentally, interruption of afferent nerve traffic by dorsal rhizotomy partially prevents hypertension in renal damage models. Imidazoline-preferring binding sites are found in the kidney. In the rat, natriuresis is elicited by injection of **moxonidine** into the renal artery. In humans, there is no definite evidence for a natriuretic effect, but some observations point in this direction. In renal disease, the issue arises whether sympathetic overactivity contributes to progression of renal failure. Indirect evidence in this direction could be the marked acceleration of progression by smoking, a state of known sympathetic overactivity. In experimental models of renal damage, **treatment** with **moxonidine** in antihypertensive doses markedly attenuated development of glomerulosclerosis. Preliminary observations show that even non-antihypertensive doses of **moxonidine** interfere with the development of glomerulosclerosis. Sympathicolytic agents are obviously rational in the antihypertensive **therapy** of the renal patient,

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because uraemia is a state of sympathetic overactivity and because blood pressure-independent effects of sympathetic activation on progression are likely.

L73 ANSWER 102 OF 137 MEDLINE
1998338620 Document Number: 98338620. PubMed ID: 9673832. Clinical pharmacokinetics of vasodilators. Part II. Kirsten R; Nelson K; Kirsten D; Heintz B. (Department of Clinical Pharmacology, University of Frankfurt, Germany. ) CLINICAL PHARMACOKINETICS, (1998 Jul) 35 (1) 9-36. Ref: 280. Journal code: DG5; 7606849. ISSN: 0312-5963. Pub. country: New Zealand. Language: English.

AB Stimulating cardiac beta 1-adrenoceptors with oxyfedrine causes dilatation of coronary vessels and positive inotropic effects on the myocardium. beta 1-adrenergic agonists increase coronary blood flow in nonstenotic and stenotic vessels. The main indication for the use of the phosphodiesterase inhibitors pamrinone, mirinone, enoximone and piroximone is acute **treatment** of severe congestive **heart failure**.
Theophylline is indicated for the **treatment** of asthma, chronic obstructive pulmonary disease, apnea in preterm infants ans sleep apnea syndrome. Severe arterial occlusive disease associated with atherosclerosis can be beneficially affected by elcosanoids. These drugs must be administered parenterally and have a half-life of only a few minutes. Sublingual or buccal preparations of nitrates are the only prompt method (within 1 or 2 min) of terminating anginal pain, except for biting nifedipine capsules. The short half-life (about 2.5 min) of nitroglycerin (glyceryl trinitrate) makes long term **therapy** impossible.
Tolerance is a problem encountered with longer-acting nitric oxide donors. Knowledge of the pharmacokinetic properties of vasodilating drugs can prevent a too sudden and severe blood pressure decrease in patients with chronic hypertension. In considering the administration of a second dose, or another drug, the time necessary for the initially administered drug to reach maximal efficacy should be taken into account. In hypertensive emergencies urapidil, sodium nitroprusside, nitroglycerin, hydralazine and phentolamine are the drugs of choice, with the addition of beta-blockers during catecholamine crisis or dissecting aortic aneurysm. Childhood hypertension is most often **treated** with angiotensin-converting enzyme (ACE) inhibitors or calcium antagonists, primarily nifedipine. Because of the teratogenic risk involved with ACE inhibitors, extreme caution must be exercised when prescribing for adolescent females. The propagation of health benefits to breast-fed infants, combined with more women delaying pregnancy until their fourth decade, has entailed an increase in the need for hypertension management during lactation. Low dose hydrochlorothiazide, propranolol, nifedipine and enalapril or captopril do not pose enough of a risk of preclude breastfeeding in this group. The most frequently used antihypertensive agents during pregnancy are methyldopa, labetalol and calcium channel antagonists. Methyldopa and beta-blockers are the drugs of choice for **treating** mild to moderate hypertension. Prazosin and hydralazine are used to **treat** moderate to severe hypertension and hydralazine, urapidil or labetalol are used to **treat** hypertensive emergencies. The use of overly aggressive antihypertensive **therapy** during pregnancy should be avoided so that adequate uteroplacental blood flow is maintained. Methyldopa is the only drug accepted for use during the first trimester of pregnancy.

L73 ANSWER 103 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1999140727 EMBASE **Sympathetic nervous system:** The link between **heart failure**, hypertension, and NIDDM: Proceedings from a satellite symposium at the XIXth congress of the European Society of Cardiology (ESC), held in Stockholm, Sweden, August 27, 1997. Introduction. Hansson L.; Mancia G.. Blood Pressure, Supplement 7/3 (4) 1998.

Searched by: Mary Hale 308-4258 CM-1 12D16

ISSN: 0803-8023. CODEN: BPSUEY. Pub. Country: Norway. Language: English.

L73 ANSWER 104 OF 137 MEDLINE
1998411667 Document Number: 98411667. PubMed ID: 9739350. [The significance of the **sympathetic nervous system** during **therapy** for hypertension and related pathologies. Imidazoline-I1-receptor agonists. 17th Scientific Meeting of the International Society of Hypertension. Amsterdam, June 7, 1998]. Die Bedeutung des sympathischen Nervensystems bei der **Therapie** der Hypertonie und verwandten Pathologien. Imidazolin-I1-Rezeptoragonisten. 17th Scientific Meeting of the International Society of Hypertension. Amsterdam, 7.Juni 1998. Anonymous. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, (1998 Aug 14) 123 (33 Suppl) 1-4. Journal code: ECL; 0006723. ISSN: 0012-0472. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

L73 ANSWER 105 OF 137 MEDLINE
1999052075 Document Number: 99052075. PubMed ID: 9835010. [Cardiovascular and metabolic diseases. Imidazolin-antagonists and the **sympathetic nervous system**]. Herz-Kreislauf- und Stoffwechselkrankheiten. Imidazolin-Agonisten und sympathisches Nervensystem. Anonymous. ZEITSCHRIFT FUR KARDIOLOGIE, (1998 Oct) 87 (10 Suppl) 1-4. Journal code: XW7; 0360430. ISSN: 0300-5860. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

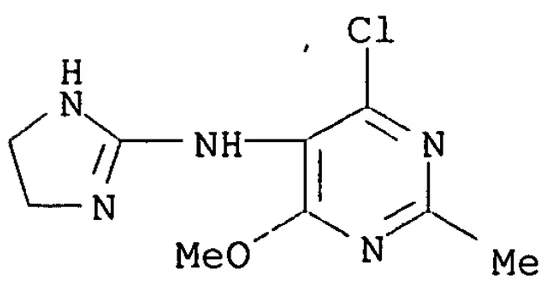
L73 ANSWER 106 OF 137 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 32
1997:812191 Document No. 128:80032 Formulation and method for **treating** congestive **heart failure**. McNay, John L. (Eli Lilly and Company, USA; McNay, John L.). PCT Int. Appl. WO 9746241 A1 19971211, 76 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US9914 19970605. PRIORITY: US 1996-659463 19960606.

AB This invention provides a method for **treating** congestive **heart failure** comprising administering an effective amt. of 4-chloro-5-(imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine (**moxonidine**) in an oral or implant nonimmediate release formulation. A controlled-release tablet was formulated contg. **moxonidine** 0.3, lactose 95.7, Povidone 0.7, Crospovidone 3, Mg stearate 0.3, hydroxypropyl Me cellulose 1.3, Et cellulose 1.2, PEG-6000 0.25, talc 0.975, red iron oxide 0.025, and titania 1.25 mg.

IT **75438-57-2, Moxonidine**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release formulations contg. **moxonidine** for **treating** congestive **heart failure**)

RN 75438-57-2 CAPLUS

CN 5-Pyrimidinamine, 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl- (9CI) (CA INDEX NAME)

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L73 ANSWER 107 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97367424 EMBASE Document No.: 1997367424. [Sympathy and heartache; news about the **sympathetic nervous system**]. MITLEID UND HERZSCHMERZ; NEUES VOM SYMPATHIKUS. Spieker L.E.; Binggeli C.; Luscher Th.F.; Noll G.. Dr. G. Noll, Kardiologie, Universitatsspital, CH-8091 Zurich, Switzerland. Schweizerische Medizinische Wochenschrift 127/48 (1986-1992) 1997.
Refs: 69.
ISSN: 0036-7672. CODEN: SMWOAS. Pub. Country: Switzerland. Language: German. Summary Language: German; English.

AB The **sympathetic nervous system** is an important regulator of the circulation. Interactions with other regulating systems, e.g. the renin angiotensin system, play important roles. By means of microneurography, sympathetic activity in humans can be assessed directly in the nerve. Insights into the dynamic regulation of the circulation under physiological and pathophysiological conditions are possible. Activation of the **sympathetic nervous system** in cardiovascular diseases affects course, prognosis, and **therapy**. Prognosis in **heart failure** depends on sympathetic activation, which can be decreased by inhibition of angiotensin II synthesis by ACE-inhibitors. In contrast to nitrates, these drugs do not increase sympathetic activity. The **sympathetic nervous system** is also heavily involved in the pathogenesis of hypertension. Borderline hypertensives and offspring of hypertensive parents show increased sympathetic nerve activities. Investigation of the **sympathetic nervous system** under physiological and pathophysiological conditions may serve as a basis for new **therapeutic** strategies.

L73 ANSWER 108 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97275966 EMBASE Document No.: 1997275966. [**Moxonidine therapy** also for elderly multimorbid patients]. MOXONIDIN: AUCH FUR ALTERE MULTIMORBIDE PATIENTEN GEEIGNET. Vollmer H.. Zeitschrift fur Allgemeinmedizin 73/12 (701) 1997.
ISSN: 0341-9835. CODEN: ZALMAS. Pub. Country: Germany. Language: German.

L73 ANSWER 109 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97356648 EMBASE Document No.: 1997356648. **Moxonidine**: A review.
Morris S.T.W.; Reid J.L.. Dr. S.T.W. Morris, The Renal Unit, Western Infirmary, Dumbarton Rd, Glasgow G11 6NT, United Kingdom. Journal of Human Hypertension 11/10 (629-635) 1997.
Refs: 58.
ISSN: 0950-9240. CODEN: JHHYEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB **Moxonidine** is an imidazoline compound which acts on I1 imidazoline 'receptors' in the central nervous system to reduce blood pressure. This novel mechanism of action is claimed to lead to fewer adverse effects than the older centrally-acting agents such as clonidine. In this review we examine the drug's pharmacology, clinical pharmacokinetics, efficacy as an antihypertensive agent including comparative studies with pre-existing drugs, and adverse effect profile. With a growing number of effective antihypertensive agents already available to the clinician, it is not yet clear whether **moxonidine** represents a significant advance in hypertension management.

L73 ANSWER 110 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97250427 EMBASE Document No.: 1997250427. [Application of captopril in **therapeutic** combination]. CAPTOPRIL FELHASZNALASA TERAPIAS KOMBINACIOKBAN. Alfoldi S.. S. Alfoldi, I Belosztaly, Fov. Szent Imre Korhaz, Tetenyi ut. 12-16, H-1115 Budapest, Hungary. Acta Pharmaceutica

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Hungarica 67/4 (149-153) 1997.
Refs: 18.
ISSN: 0001-6659. CODEN: APHGAO. Pub. Country: Hungary. Language: Hungarian. Summary Language: Hungarian; English.

AB The importance of captopril in the combined drug **treatment** of hypertension, congestive **heart failure** and ischemic heart disease is reviewed.

L73 ANSWER 111 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97066434 EMBASE Document No.: 1997066434. [Hypertension: **Therapy** not yet sufficient]. HYPERTONIE: **THERAPIE** NOCH NICHT BEFRIEDIGEND. Vetter C.. Pharmazeutische Zeitung 142/6 (64) 1997.
ISSN: 0031-7136. CODEN: PZSED5. Pub. Country: Germany. Language: German. Summary Language: German.

L73 ANSWER 112 OF 137 MEDLINE
97462953 Document Number: 97462953. PubMed ID: 9321737. Pharmacology and clinical use of **moxonidine**, a new centrally acting sympatholytic antihypertensive agent. Prichard B N; Owens C W; Graham B R. (Division of Clinical Pharmacology and Toxicology, University College London Medical School, UK. ) JOURNAL OF HUMAN HYPERTENSION, (1997 Aug) 11 Suppl 1 S29-45.
Ref: 78. Journal code: JYT; 8811625. ISSN: 0950-9240. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Moxonidine** is a centrally acting antihypertensive. Its action is mediated by imidazoline I1 receptors located in the rostral ventro-lateral medulla (RVLM). Animal experiments show much smaller amounts are required to reduce blood pressure (BP) when it is given intracisternally, or injected directly into the RVLM, compared to intravenous dose. The antihypertensive action of microinjection of **moxonidine** into the RVLM in the spontaneously hypertensive rat (SHR) is abolished by pretreatment with imidazoline I1 blockade from efaroxan, but alpha(2) blockade from SKF 86466 has much less effect. Similarly the fall of BP in the SHR from intravenous **moxonidine** is reversed by the microinjection of efaroxan into the RVLM. Receptor binding studies demonstrate that **moxonidine** binds with an affinity for the imidazoline I1 receptor that is thirty-three times more effective than is alpha(2) receptor binding, while for clonidine the difference is only four times. **Moxonidine** reduces adrenaline, noradrenaline and renin levels in man, a finding consistent with central inhibition of sympathetic tone. Acute haemodynamic studies indicate that **moxonidine** results in a fall of BP due to a decline in systemic vascular resistance, while the heart rate, cardiac output, stroke volume and pulmonary artery pressures are not affected. Left ventricular end systolic and diastolic volumes are reduced. Left ventricular hypertrophy has been found to regress after 6 months **treatment** with **moxonidine**.
After oral administration Tmax is about 1 h, bioavailability approaches 90%. **Moxonidine** is mostly excreted unchanged, biotransformation is unimportant. The T1/2 is 2.5 h, which is prolonged by renal insufficiency. However, suggesting possible retention in the central nervous system (CNS), the antihypertensive effect lasts longer than would be expected from the half-life, as **moxonidine** is suitable for once daily administration. **Moxonidine** is an effective antihypertensive agent. It has been compared with representatives from each important class of antihypertensive drugs, with clonidine, diuretics, both alpha- and beta-blocking drugs, calcium antagonists and ACE inhibitors. BP control has been similar with **moxonidine** and these other agents. The side effect profile of **moxonidine** is favourable, its lack of effect on central alpha(2) receptors is important in this regard.

L73 ANSWER 113 OF 137 MEDLINE
97471637 Document Number: 97471637. PubMed ID: 9330578. [Moxonidin in

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**heart failure**: new **therapeutic** principles suppress neurohumoral activation. Supplement to the Congress on " **Heart Failure**" of the working group on cardiac insufficiency at the European Society for Cardiology. Cologne, May 1997]. Moxonidin bei Herzinsuffizienz: Neue **Therapieprinzipien** dampfen die neurohumorale Aktivierung. Beilage zum Kongress "**Heart Failure**" der Arbeitsgruppe zur Herzinsuffizienz der Europaischen Gesellschaft fur Kardiologie. Koln, im Mai 1997. Anonymous. DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT, (1997 Sep) 122 (36 Suppl Moxonidin) 1-4. Journal code: ECL; 0006723. ISSN: 0012-0472. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

L73 ANSWER 114 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97032760 EMBASE Document No.: 1997032760. [**Moxonidine** - A modern **therapy** concept for lowering of the sympathoadrenergic activity and for the **treatment** of arterial hypertension]. MOXONIDIN - EIN NEUARTIGES **THERAPIEKONZEPT** ZUR SENKUNG DER SYMPATHOADRENERGEN AKTIVITAT UND ZUR BEHANDLUNG DER ARTERIELLEN HYPERTONIE. Schwinger R.H.G.. Herz Kreislauf 29/SUPPL. 1 (1-4) 1997.
ISSN: 0046-7324. CODEN: HZKLAV. Pub. Country: Germany. Language: German.
Summary Language: German.

L73 ANSWER 115 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998027928 EMBASE [News on pharmacotherapy of coronary heart disease, **heart failure** and hypertension]. NEUES ZUR PHARMAKOTHERAPIE DER KHK, HERZINSUFFIZIENZ UND HYPERTONIE. Glaser W.. Klinikarzt 26/12 (X-XIII) 1997.
ISSN: 0341-2350. CODEN: KLINFZ. Pub. Country: Germany. Language: German.

L73 ANSWER 116 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
96186979 EMBASE Document No.: 1996186979. [Ideal blood pressure lowering]. IDEALE BLUTDRUCKSENKUNG. Philipp T.. Universitatsklinik,Essen, Germany. Therapiewoche 46/20 (1086-1087) 1996.
ISSN: 0040-5973. CODEN: THEWA6. Pub. Country: Germany. Language: German.
Summary Language: German.

L73 ANSWER 117 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
96122039 EMBASE Document No.: 1996122039. [**Moxonidine**: Possible alternative for beta blockade in **heart failure**?].
MOXONIDIN: MOGLICHE ALTERNATIVE ZUR BETABLOCKADE BEI HERZINSUFFIZIENZ?. Therapiewoche 46/12 (682) 1996.
ISSN: 0040-5973. CODEN: THEWA6. Pub. Country: Germany. Language: German.
Summary Language: German.

L73 ANSWER 118 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
96122034 EMBASE Document No.: 1996122034. [Sympathetic nerve activity and hypertension]. SYMPATHIKUSAKTIVITAT UND BLUTHOCHDRUCK. Therapiewoche 46/12 (671-672) 1996.
ISSN: 0040-5973. CODEN: THEWA6. Pub. Country: Germany. Language: German.

L73 ANSWER 119 OF 137 MEDLINE DUPLICATE 33
96425560 Document Number: 96425560. PubMed ID: 8827950.
**Sympathetic nervous system** in salt-sensitive and obese hypertension: amelioration of multiple abnormalities by a central sympatholytic agent. Ernsberger P; Koletsky R J; Collins L A; Bedol D. (Department of Medicine, Case Western Reserve School of Medicine and St. Luke's Medical Center, Cleveland, Ohio, USA. ) CARDIOVASCULAR DRUGS AND THERAPY, (1996 Jun) 10 Suppl 1 275-82. Journal code: AYG; 8712220. ISSN: 0920-3206. Pub. country: United States. Language: English.
AB Excess activity of the **sympathetic nervous system** (SNS) is linked to human obese hypertension and to salt-sensitive hypertension. Paradoxically, reduced SNS activity has been

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implicated as a contributor to obesity, particularly in animal models, and salt loading usually inhibits SNS activity. We have investigated the relationship between SNS activity, diet, and hypertension in the obese spontaneously hypertensive rat (SHROB), a model with a recessive obesity trait superimposed on a hypertensive background with multiple metabolic abnormalities resembling human syndrome X. We examined the role of SNS overactivity in the adverse impact of excess dietary salt and the possible beneficial effects of sympatholytic **therapy**. Mean blood pressure (MBP) was increased in SHROB and SHR fed a 4% NaCl diet. The pressor effect of dietary salt was abolished by ganglionic blockade, suggesting that increased SNS activity contributed to the pressor effect of the high-salt diet. **Moxonidine**, a second-generation central antihypertensive, controlled hypertension in both SHROB and SHR. Kidney damage in SHROB was accelerated by dietary salt and was reduced by **moxonidine**. **Moxonidine** elicited progressive weight loss in SHROB but not in SHR. Food intake in SHROB was reduced to the level of lean SHR. SHROB and SHR **treated** with **moxonidine** showed improved glucose tolerance. Additionally, SHROB showed reduced levels of triglycerides, cholesterol, and insulin following **moxonidine** **therapy**. Inhibition of the SNS, as with **moxonidine** **therapy**, may ameliorate multiple abnormalities and have **therapeutic** advantages in obese hypertensive syndromes.

L73 ANSWER 120 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
96208228 EMBASE Document No.: 1996208228. New **therapeutic** agents for hypertension. Reid J.L.. Prof. J.L. Reid, Dept. of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, United Kingdom. British Journal of Clinical Pharmacology 42/1 (37-41) 1996.
ISSN: 0306-5251. CODEN: BCPHBM. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB 1. Over the last 40 years a range of **therapeutic** strategies has been introduced for the long term **treatment** of hypertension. 2. Although safe effective agents are available a significant number of patients are unable or unwilling to take these drugs as long term **treatment**. 3. Both insufficient efficacy and adverse effects justify the search for new antihypertensive strategies. 4. Recent developments include orally active angiotensin (AT1) receptor antagonists (ARA) which appear to offer the benefits of prevention of angiotensin II effects without the adverse effects of bradykinin potentiation, such as cough, which limit the usefulness of angiotensin converting enzyme (ACE) inhibitors. 5. Imidazoline receptor agonists offer the potential of centrally active antihypertensives without the adverse effects of sedation and dry mouth. Further clinical experience is necessary to confirm whether the clinical efficacy and good tolerability are confirmed with long term use. 6. Both ARA and imidazoline preferring substances offer the bonus of a desirable haemodynamic profile in patients with **heart** **failure** and may open new **therapeutic** avenues in the management of cardiac failure.

L73 ANSWER 121 OF 137 MEDLINE DUPLICATE 34
97026118 Document Number: 97026118. PubMed ID: 8872297. Pharmacology of **moxonidine**, an I1-imidazoline receptor agonist. Ziegler D; Haxhiu M A; Kaan E C; Papp J G; Ernsberger P. (Research and Development, Solvay Pharma Deutschland, Hannover, Germany. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1996) 27 Suppl 3 S26-37. Ref: 52. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.
AB **Moxonidine** is a second-generation, centrally acting antihypertensive drug with a distinctive mode of action. **Moxonidine** activates I1-imidazoline receptors (I1-receptors) in the rostroventrolateral medulla (RVLM), thereby reducing the activity of the **sympathetic nervous system**.

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**Moxonidine** leads to a pronounced and long-lasting blood pressure reduction in different animal models of hypertension, e.g., spontaneously hypertensive rats, renal hypertensive rats, and renal hypertensive dogs. Blood pressure reduction with **moxonidine** is usually accompanied by a reduction in heart rate which, however, in most studies is of shorter duration and lesser magnitude than the fall in blood pressure. Chronic administration of **moxonidine** to SHRs with established hypertension causes normalization of myocardial fibrosis, capillarization, and regressive changes in myocytes, in parallel with the reduction of blood pressure. Left ventricular hypertrophy and renal glomerulosclerosis are also significantly reduced. After withdrawal of chronic **moxonidine treatment**, blood pressure gradually rises to pretreatment values. Direct injection of **moxonidine** into the vertebral artery of cats elicits a more pronounced fall in blood pressure compared with i.v. injection of an equivalent dose. This observation and others clearly indicate that **moxonidine**'s antihypertensive activity is centrally mediated. The RVLM is the site of action within the CNS that mediates pronounced blood pressure reduction after direct administration of **moxonidine** into the RVLM of anesthetized SHRs. Selective I1-receptor antagonists introduced into this area abolish the action of systemic **moxonidine**. Receptor binding studies have shown high and selective affinity of **moxonidine** for I1-receptors vs. alpha(2)-adrenergic receptors. In vivo studies using a variety of selective I1 or alpha(2)-adrenergic agonists and antagonists have confirmed the primary role of I1-receptors in blood pressure regulation by **moxonidine**. In addition to lowering blood pressure, **moxonidine** possesses further properties that appear likely to be relevant in its **therapeutic** application in the hypertensive syndrome. **Moxonidine** increases urine flow rate and sodium excretion after central and direct intrarenal administration. It is active against ventricular arrhythmias in a variety of experimental settings. It lacks the respiratory depressant effect attributed to central alpha 2 activation. It exerts beneficial effects on glucose metabolism and blood lipids in genetically hypertensive obese rats. It exhibits anti-ulcer activity. And, finally, **moxonidine** lowers intraocular pressure, suggesting a possible benefit in glaucoma. Therefore, **moxonidine** , by its novel mode of action, represents a new **therapeutic** principle in the **treatment** of hypertension. Because of its unique profile, **moxonidine** may prove to be effective in slowing progression of the disease by providing protective effects beyond merely blood pressure reduction. Further studies are needed to verify this potential.

L73 ANSWER 122 OF 137 MEDLINE DUPLICATE 35
97026115 Document Number: 97026115. PubMed ID: 8872294. From alpha and beta to I1: an overview of sympathetic receptors involved in blood pressure control targets for drug **treatment**. van Zwieten P A. (Department of Pharmacotherapy, Academic Medical Center, University of Amsterdam, The Netherlands. ) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1996) 27 Suppl 3 S5-10. Ref: 36. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB There is no doubt that the **sympathetic nervous system** (SNS) plays an important role in the pathogenesis and maintenance of hypertensive disease, although many details concerning this association remain to be clarified. Over the years, several types of antihypertensive drugs have been developed that can impair SNS activity at virtually all levels of the system. Alpha and beta-adrenoceptor antagonists, postganglionic sympathetic neuron blockers and ganglioplegic agents are well-known examples of drugs with a predominantly peripheral activity. The CNS regulation of peripheral sympathetic activity offers a further possibility to counteract the influence of SNS activity. In particular, central catecholaminergic neurons and alpha-adrenoceptors have

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been analyzed in detail and are recognized as important targets for the classic centrally acting antihypertensives clonidine, guanfacine, and alpha-methyldopa. Initially, these drugs were assumed to reduce elevated blood pressure via the stimulation of central alpha-adrenoceptors in the brainstem, thus leading to peripheral sympathoinhibition and a reduction of elevated blood pressure, heart rate, and plasma catecholamines. In a later stage it has been recognized that central imidazoline (I1) receptors may also be involved in the central regulation of peripheral sympathetic activity and that they act as a target for centrally acting antihypertensives. **Moxonidine** and rilmenidine are the prototypes of such agents. Accordingly, the receptor profile of the various types of centrally acting antihypertensives can be characterized as follows: alpha-methyl-DOPA (through alpha-methyl-norepinephrine) alpha 2; clonidine (mixed agonist), alpha 2 + I1; **moxonidine**, rilmenidine, I1 > alpha 2. The various compounds mentioned will thus cause peripheral sympathoinhibition, initiated by different receptor targets in the CNS. Because most of the adverse reactions to clonidine and related drugs are mediated by central alpha-adrenoceptors, is is hoped that the imidazoline receptor agonists (**moxonidine**, rilmenidine) will show a more favorable pattern of side effects.

L73 ANSWER 123 OF 137 MEDLINE DUPLICATE 36

95407887 Document Number: 95407887. PubMed ID: 7677385. Why imidazoline receptor modulator in the **treatment** of hypertension?. Schafer S G; Kaan E C; Christen M O; Low-Kroger A; Mest H J; Molderings G J. (Solvay Pharma Germany, Hanover. ) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1995 Jul 12) 763 659-72. Ref: 64. Journal code: 5NM; 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB The influence of the **sympathetic nervous system** on blood pressure control was impressively demonstrated in 1940 by bilateral excision of sympathetic nerve fibers. Thereafter, the first generation of drugs lowering blood pressure by central modulation of the sympathetic outflow through alpha 2-adrenoceptor for stimulation, such as alpha-methyldopa, guanabenz, clonidine, and guanfacine, were marketed. However, these compounds were often tolerated poorly, because they caused orthostatic hypotension, sedation, tachycardia or bradycardia, dry mouth, and reduced cardiac output. The mode of action of the second generation centrally acting antihypertensive drugs **moxonidine** and rilmenidine is different from that of the first generation compounds (e.g., clonidine). Contrary to clonidine, the newer drugs bind more selectively to I1-imidazoline receptors rather than to alpha 2-adrenoceptors where first-generation drugs act. The high affinity and selectivity of these two drugs for this recently discovered new receptor class make it possible to discriminate between I1-imidazoline receptor-mediated blood pressure lowering, on the one hand, and alpha 2-adrenoceptor-mediated side effects, on the other. Discrimination of the two effects was substantiated either by studies using **moxonidine** alone or in interaction experiments with I1-imidazoline receptor or alpha 2-adrenoceptor antagonists. The high selectivity of **moxonidine** at the I1-imidazoline receptor allows discrimination between alpha 2-adrenoceptors and I1-imidazoline receptors and is reflected in man by the relatively low incidence of adverse drug events during **moxonidine treatment**. Concentration of endazoline, a specific mediator of I1-imidazoline receptors, is elevated in some patients with essential hypertension. Modulation of I1-imidazoline receptors by **moxonidine** could be interpreted as antagonism with regard to the endogenous agonistic effect of the endogenous "transmitter" endazoline. On the other hand, **moxonidine** acted directly as an agonist at the putative I1-imidazoline receptor. Therefore, to clear the ground, characterization as well as physiological function of the mediator for imidazoline receptors seems essential. The **therapeutic** relevance of using drugs selective for I1-imidazoline receptors for blood

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pressure reduction in hypertensive patients is substantiated by the finding that in human rostral ventrolateral medulla (RVLM), which is essential in central blood pressure regulation, the relation between alpha 2-adrenoceptors and I1-imidazoline receptors is about one to ten (1:10). Reduction of a long-lasting sympathetic overdrive may avoid the deteriorating effects on the heart and peripheral circulation. These recent findings give a rational explanation for the very low incidence of sedation and the absence of respiratory depression, orthostatic hypotension, and rebound hypertension that banned the former central acting antihypertensive drugs from first-line **treatment** despite the advantages of central mediated blood pressure control.

L73 ANSWER 124 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
95319215 EMBASE Document No.: 1995319215. Reports from the XVII Congress of the European Society of Cardiology, Amsterdam. British Journal of Cardiology 2/9 (262-265) 1995.
ISSN: 0969-6113. CODEN: BJCAEM. Pub. Country: United Kingdom. Language: English.

L73 ANSWER 125 OF 137 MEDLINE
95333964 Document Number: 95333964. PubMed ID: 7609678. Excess catecholamines and the metabolic syndrome: should central imidazoline receptors be a **therapeutic** target?. Rupp H; Jacob R. (Molecular Cardiology Laboratory, University of Marburg, Germany. ) MEDICAL HYPOTHESES, (1995 Mar) 44 (3) 217-25. Ref: 86. Journal code: M0M; 7505668. ISSN: 0306-9877. Pub. country: ENGLAND: United Kingdom. Language: English.
AB A sympathetic overactivity plays a major role in the pathogenesis of cardiovascular diseases in Westernized affluent societies. Of importance is an increased caloric intake and psychosocial stress which are associated with a raised central sympathetic outflow and unfavourable changes in metabolic parameters. Normalization of central sympathetic outflow could thus be a major **therapeutic** target. The newly developed antihypertensive drugs **moxonidine** and rilmenidine reduce the excitatory activity of neurons of the rostral ventrolateral medulla (RVLM) via binding to imidazoline receptors. Using radio telemetry, it is shown that, in contrast to the first generation centrally acting drug clonidine, **moxonidine** did not result in rebound of blood pressure after drug withdrawal in rats with spontaneous hypertension. In accordance, **moxonidine** is characterized by a low affinity for alpha-adrenoceptors and exhibits few side-effects. It is proposed that normalization of central sympathetic outflow represents a causal approach for improving crucial features of the metabolic syndrome.

L73 ANSWER 126 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
94363661 EMBASE Document No.: 1994363661. [Indication for centrally acting antihypertensive agents]. INDIKATION FUR ZENTRALE ANTIHYPERTENSIVA. Filip K.B.. Therapiewoche 44/37 (2179-2180) 1994.
ISSN: 0040-5973. CODEN: THEWA6. Pub. Country: Germany. Language: German.

L73 ANSWER 127 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
94364218 EMBASE Document No.: 1994364218. I1-imidazoline-receptor agonists in the **treatment** of hypertension: An appraisal of clinical experience. Ollivier J.-P.; Christen M.O.. Department of Cardiology, HIA du Val-de-Grace,F-75230 Paris Cedex 05, France. Journal of Cardiovascular Pharmacology 24/SUPPL. 1 (S39-S48) 1994.
ISSN: 0160-2446. CODEN: JCPCDT. Pub. Country: United States. Language: English. Summary Language: English.
AB Although essential hypertension is usually defined as a hemodynamic disorder, it is expressed differently among individuals and varies during progression of the disease state. Therefore, various types of **treatment** can be envisioned. The use of selective

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I1-imidazoline-receptor agonists to modulate I1-imidazoline receptors involved in the central regulation of blood pressure has led to the introduction of a novel class of centrally acting antihypertensive drugs. **Moxonidine**, a representative molecule of this class, dissociates between a 10% .alpha.2-adrenoceptor agonist action linked with side effects such as fatigue or dry mouth, and a 90% specific antihypertensive action resulting from its selective agonistic action at I1- imidazoline receptors. Clinical experience is based on more than 2,000 patients and volunteers, and long-term efficacy has been demonstrated in about 500 patients who received a daily dose of **moxonidine** 0.2-0.4 mg. **Moxonidine** produces a pronounced reduction in peripheral vascular resistance without reflex tachycardia, accompanied by reduced plasma norepinephrine concentration and plasma renin activity. Cardiovascular responses to exercise and standing remain nearly normal, and serious or life threatening side effects, particularly the sympathetic overactivity that can occur on sudden withdrawal of other centrally acting agents, are never observed. In addition, **moxonidine** behaves neutrally with respect to plasma levels of cholesterol, potassium and glucose, glucose and lipid metabolism, and renal function, and can be administered without complication to patients with asthma or certain other diseases. Studies with magnetic resonance imaging have shown that **moxonidine** significantly reduces left ventricular mass, an indicator of left ventricular hypertrophy (LVH), within a 6-month **treatment** period, an effect that coincided with decreased plasma concentrations of catecholamines and renin. Comparisons between **moxonidine** and other well-established antihypertensive drugs such as nifedipine, atenolol, or angiotensin- converting enzyme inhibitors showed equal effectiveness in lowering blood pressure, whereas the adverse events profile always favored **moxonidine**. Considering its efficacy, safety, and specific effects (e.g., its ability to reduce LVH), **moxonidine** meets the criteria satisfied by other currently prescribed antihypertensive drugs. Because of its especially favorable benefit-to-risk ratio, **moxonidine** should be recommended as first-line **treatment** of hypertension and may also be useful in **treating** related problems such as LVH, coronary artery disease, and ventricular premature beats.

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Language: English.
AB Research on antihypertensive drugs not only provides new information on presently used agents but also leads to the introduction of exciting new compounds. Several important clinical trials involving currently available drugs have been published recently. Angiotensin-converting enzyme inhibitors improved survival in patients with milder degrees of congestive **heart failure**, which indicates that they have become the cornerstone of **treatment** for this condition.
Angiotensin-converting enzyme inhibitors delayed or prevented the development of diabetic proteinuria (> 200 micrograms/min) in a placebo-controlled randomized trial. Further, enalapril was more effective than metoprolol in reducing the rate of decline in renal function in patients with type I diabetes. Calcium channel blockers protected against acute renal failure in patients after renal transplantation in two separate studies. Calcium channel blockers were shown to promote natriuresis, with negative sodium balance the same as that associated with thiazide diuretics. The voltage-dependent calcium channel has been cloned, and the binding sites of the three classes of calcium channel blockers are now known. beta-Blockers and thiazide diuretics were the drug **treatments** in the Systolic Hypertension in the Elderly Program trial and in the Swedish Trial in Old Patients with Hypertension study (patients 65 to 85 years). In both investigations, stroke and cardiovascular events were significantly reduced by these conventional inexpensive agents. Clonidine was found to lower blood pressure primarily by its interaction with the imidazole receptor rather than the alpha 2 receptor. Elucidation of the imidazole receptor promises to shed light on physiologic mechanisms as well as lead to the introduction of new agents, such as **moxonidine**.(ABSTRACT TRUNCATED AT 250 WORDS)

L73 ANSWER 134 OF 137 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
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left ventricular hypertrophy by different antihypertensive drugs. Motz W.; Strauer B.E.. Medizinische Klinik/Poliklinik B, Abteilung Kardiologie, Angiologie, Universitat Dusseldorf, Moorenstrasse 5,W-4000 Dusseldorf 1, Germany. Clinical Investigator, Supplement 70/2 (S87-S92) 1992.
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Summary Language: English.

AB Left ventricular hypertrophy (LVH) constitutes a powerful independent risk factor in hypertensive heart disease. Although initially the wall stress, i.e., left ventricular afterload, remains normal, the coronary reserve is diminished due to disturbances in the microcirculation. This is also shown in the commonly present silent ischemia episodes in Holter monitoring. LVH also causes ventricular dilation and **heart failure**.
Apart from systolic wall stress LVH is modulated by the trophic effects of the **sympathetic nervous system** and
angiotensin II and genetic factors. Long-term antihypertensive **treatment** must therefore focus on regression of both LVH and the microvascular abnormalities. A step approach for the **treatment** of the LVH has been recommended on the basis of the experience of this working group with calcium antagonists and ACE inhibitors, whereas the place of .beta.-blockers is as yet unclear. Preliminary data indicate that coronary flow rescue can also be improved after chronic antihypertensive **treatment**.

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AB A review with 55 refs. discussing how novel centrally acting antihypertensive agents such as **moxonidine** and rilmenidine have been used in the **treatment** of hypertension.

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